

OLA OHLSSON

**HAEMODYNAMIC STUDIES OF RELATIVES
TO HYPERTENSIVE PATIENTS**

**A study on relatives to families with a high
frequency of essential hypertension**



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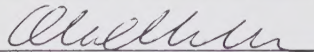
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Abstract From 106 hypertensive individuals with two generations suffering from essential hypertension, 1181 family members were traced. The occurrence of hypertension was close to 50% among the family members. A total of 307 were compared to controls without known hypertension in their families. Systolic blood pressure, heart rate and plasma albumin concentration were significantly higher in the family members. In subgroups the difference in blood pressure and heart rate found at rest was maintained during several tests. Blood pressure was found to be stronger related to age in relatives than in controls. The elevated blood pressure in relatives was not associated with an increased cardiac output, indicating an increased peripheral vascular resistance. Arterial blood pCO ₂ was lower in relatives than in controls. Blood pH and standard bicarbonate did not differ between the groups. Total plasma volume was significantly lower, the quotient central/total plasma volume was higher in relatives as compared to controls. This difference in the plasma distribution could not be explained by differences in venous capacitance in skin tissue. Plasma catecholamines were almost equal in both groups, norepinephrine was even found to be significantly lower in the relatives during cold pressure test.		
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A study on relatives to families with a high frequency of
essential hypertension

By

Ola Ohlsson

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with a high frequency of essential hypertension.
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*To
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INTRODUCTION

Epidemiological and clinical studies have demonstrated a greatly increased mortality and morbidity in cardiovascular diseases among individuals with high blood pressure (25, 50, 51, 52). Mortality and morbidity rise as both when the systolic and diastolic blood pressure rise (24). When the conventional limit between normal and high blood pressure is used, around 10% of a middle aged population has been found to need treatment for hypertension (36, 53). In such studies it has been estimated that 95% of individuals with high blood pressure have an essential hypertension (EH), i.e. hypertension without known etiology (6, 16). This should not lead to the conclusion that secondary forms of hypertension are of little importance. They may be even more than 5% since mass investigations can only make superficial exclusions of secondary forms of hypertension and renal hypertensives are usually already having specialist treatment.

To elucidate mechanisms of the high blood pressure, several haemodynamic studies have been performed on individuals with established EH. These individuals were found to have a decreased cardiac output and an increased peripheral vascular resistance, both at rest and during exercise, as compared to controls with normal blood pressure (1, 46, 49). A decreased plasma volume was reported in EH by Wollheim in 1960 (55), and this has been verified by many other authors (20, 37, 45, 47). An increased ratio central/total plasma volume has also been described in EH (48). One must, however, take into consideration that these changes could be the result of the high blood pressure rather than the mechanisms causing the disease. Prehypertensive and early hypertensive phases of EH have mainly been studied in so-called "borderline or labile" hypertensive subjects. They have been reported to have an increased cardiac output at rest, but a normal peripheral vascular resistance. During exercise, cardiac output has been found to be almost equal to that of normotensive individuals (21, 22, 29, 38). Also in borderline hypertensives a decreased total plasma volume and an increased ratio central/total plasma volume have been reported (11, 23, 40). It is, however, doubtful whether individuals with borderline hypertension really do represent a prehypertensive state, since the risk of developing established EH varies considerably between different studies, from no increased risk to the double (21).

It is, however, known that relatives to hypertensive individuals have a 3-4 fold excess risk of becoming hypertensives vs. the general population, also when rather wide blood pressure criteria for hypertension are employed (2, 34, 42). Familial aggregation of essential hypertension has been described previously (31, 55) and the occurrence of hypertension and hypertensive diseases in those families has been reported to be around 40-50% (2, 17, 34, 55, 57). A cross-sectional study of members of such families will give a wide spectrum of different phases in the development of hypertension and also the possibilities of studying haemodynamic and metabolic changes in individuals prone to later EH.

The first step in this investigation was aimed at finding families with a high frequency of hypertension (Paper I). In the following steps, we investigated members of those families with regard to:

1. Blood pressure and heart rate as well as some chemical variables in relatives of hypertensive patients (Paper I).
2. Changes in blood pressure and heart rate during static muscle work, psychological stress and dynamic muscle work (Paper II).
3. Haemodynamic characteristics (cardiac output, stroke volume and peripheral vascular resistance) studied with invasive methods at rest, during static muscle work, cold pressure test, psychological stress and dynamic muscle work (Paper III).
4. Plasma volume and its distribution at rest, during static muscle work, cold pressure test, psychological stress and dynamic muscle work (Paper IV).
5. Plasma levels of catecholamines and plasma renin activity at rest, during static muscle work, cold pressure test and psychological stress (Paper V).
6. Venous volume and blood flow in the hand at rest and during a psychological stress test (Paper VI).

MATERIAL

By investigating consecutive records of patients treated at the Department of Medicine, Malmö General Hospital, 106 hypertensive individuals (probands) aged 20-60 years, all belonging to families with at least two generations suffering from EH, were traced. Patients with manifest diabetes or secondary hypertension were not included in the study. From these probands, 1075 relatives were traced, 787 of whom were alive. The family members, aged 20-60 years, living in the city of Malmö or its surroundings, were invited to a further investigation, provided they were not having treatment for hypertension. A total of 339 family members were invited, 7 refused to come. Of the 332 individuals, who participated in the study, 25 were found to be on antihypertensive drugs and 307 (169 males and 138 females) remained for the first study (I).

All individuals from the first study were invited to further investigation of blood pressure and heart rate during different tests (II). A total of 195 relatives accepted (114 males and 81 females).

The more complicated invasive studies of the relatives (III-V) were limited to males, who were the offspring of hypertensive subjects in families, where the occurrence of hypertension was at least 50% among the family members. For the study of blood flows and venous volume in the hand we selected those individuals who had the lowest plasma volume in paper IV, as the purpose of that investigation was to study the association between changes in plasma volume and venous volume.

The controls were recruited from hospital staff members and firemen. They had had no known hypertension in their families for at least two generations and were called "genetic controls" in this study. It was not necessarily the same controls, who were recruited for the different studies, many of them took part only in one study. In this way they differed from the relatives, as those who had taken part in studies III, IV, V and VI, also participated in studies I and II. In paper I, we also compared the relatives with aged and sex matched cohorts from the screened population from the Department of Preventive Medicine.

METHODS

Blood pressure and heart rate

In the first study on 307 relatives (I), all blood pressures and heart rates were recorded by the same nurse at the same time of the day, between 1 and 3 p.m. Blood pressure was measured with an appropriate arm cuff in both arms with a mercury manometer after exactly 10 minutes' rest in the supine position. The highest value of the two registrations in the arms was used in this study. In the following studies on sub-groups of the relatives, all blood pressure registrations were performed in the morning, 8-10 a.m. but were measured by different staff members each time. In all studies we used Korotkoff's phase V as the diastolic blood pressure. In those cases, where phase V could not be clearly defined, Korotkoff's phase IV was used. Invasive blood pressure registrations reported in papers III-V were performed with an electromanometer (Siemens-Elema nr EMT 746), using a polyethylene catheter (PE 160) inserted into the brachial artery.

Biochemical parameters

All blood samples were taken in the morning after 8 hours' fasting. All routine laboratory tests were performed at the Department of Clinical Chemistry, Malmö General Hospital.

Haemodynamic parameters

The haemodynamic measurements were performed at the Department of Clinical Physiology, Malmö General Hospital. These are described in detail in papers II-VI.

Statistical methods

Standard statistical methods were used for calculations of mean values, standard deviations and correlation coefficients. For comparison between means of two groups Student's t-test was used.

RESULTS

Occurrence of EH and hypertensive diseases in the families studied (Paper I)

In the 106 families studied a total of 1181 family members were traced and 332 investigated. The occurrence of hypertension was found to be close to 50% in this material. Of the deceased family members, who were exclusively parents or siblings of probands, 52% had died from stroke before 65 years of age.

Blood pressure and heart rate at rest

Mean systolic blood pressure was significantly higher among male and female relatives of all ages as compared to the controls. Mean diastolic blood pressure was significantly higher only among female relatives older than 40 years as compared to age matched controls. Mean heart rate was significantly higher among both male and female relatives of all ages as compared to controls.

Height and weight

There were no significant differences in height and weight between relatives and controls. There was no correlation between body mass index (BMI) and blood pressure in relatives. However, in genetic controls a significant correlation between systolic blood pressure and BMI was found in males ($r = 0.36$; $p < 0.05$).

Laboratory investigations

Plasma albumin was significantly higher in male and female relatives of all ages as compared to controls. There were no systematic differences between relatives and controls in hemoglobin, hematocrit, creatinin or s-GT.

Correlation between the variables studied

A significant correlation between systolic blood pressure and plasma albumin concentration was found in young male and female relatives ($r = 0.25$; $p < 0.01$ and $r = 0.33$, $p < 0.001$, respectively). No correlation between these variables was found in controls. There was a weak but significant correlation between s-GT and systolic blood pressure in both male and female relatives ($r = 0.24$; $p < 0.01$) but not in controls.

Blood pressure and heart rate at rest, static muscle work, psychological stress and dynamic muscle work (Paper II)

A sub-group of all relatives investigated in study I, consisting of 195 individuals (114 males and 81 females) was investigated with non-invasive measurement of blood pressure during static muscle work, psychological stress and dynamic muscle work, as well as ECG recordings during these procedures. The relatives were compared to 44 male and 24 female genetic controls. We found that systolic blood pressure had decreased by 6 mmHg in males ($p < 0.01$) from the first investigation (I) to the present one, heart rate had decreased by 3/min (n.s.). Diastolic blood pressure decreased by 1 mmHg (n.s.). Corresponding decrease in systolic and diastolic blood pressure in females was 2 mmHg (n.s.), heart rate 3/min (n.s.). During the tests, the difference between relatives and controls found at rest in blood pressure and heart rate, were maintained, both during and after the procedures. At dynamic muscle work, the differences in blood pressure between relatives and controls were maintained up to sub-maximal work. The differences between the groups decreased as maximal work was approached.

Obviously, many relatives from hypertensive families have blood pressures entirely within the range of the controls. For this reason it seemed desirable to analyse in what way the relatives with the highest blood pressures differed from those with the lowest blood pressures. The relatives were thus divided into quartiles as regards systolic blood pressure at rest. In this analysis we found that the quartiles of male and female relatives with the highest systolic blood pressure were significantly older and also had a higher diastolic blood pressure and heart rate at rest and during all procedures as compared to the quartile with the lowest systolic blood pressure at rest. The blood pressure response to the tests performed was practically identical in the quartile with the lowest systolic blood pressure at rest as compared to the quartile with the highest systolic blood pressure at rest. We also subdivided relatives and controls into age groups <40 years of age and ≥ 40 years of age. The most interesting finding was that there was no significant difference between relatives and controls in systolic and diastolic blood pressure in the youngest age group either at rest or during the procedures. In the age group ≥ 40 years, a significantly higher systolic blood pressure ($p < 0.001$) and diastolic blood pressure ($p < 0.01$) at rest were found in relatives as compared to controls. These differences between the groups were roughly maintained during the procedures. When comparing blood pressures between older and younger relatives, a significantly higher systolic

blood pressure ($p < 0.001$) and diastolic blood pressure ($p < 0.01$), but not heart rate (n.s.), were found among the older relatives as compared to the youngest group, both at rest before and during the tests. No significant differences were found among the controls.

In order to make it possible to compare the reaction of blood pressure and heart rate to the various stimuli and in order to be able to disregard the effects of age and blood pressure, we formed two groups with exactly blood pressure and age matched relatives and controls. When matching according to systolic blood pressure and age, we formed 25 pairs of relatives and controls, mean age 33 years. The rise in blood pressure and heart rate, caused by the stimuli did not differ between relatives and controls. Subdividing these matched pairs of relatives and controls into older and younger relatives (mean age 40 and 27 years, respectively) and older and younger controls (mean age 39 and 26 years, respectively), no significant difference was found between the groups, either at rest or during the tests. When matching according to diastolic blood pressure and age, 32 pairs of relatives and controls were formed, mean age 34 years. No difference in blood pressure or heart rate was found between relatives and controls during or after the tests. Here too, we arranged two series according to age, older and younger relatives (mean age 39 and 27 years) and older and younger controls (mean age 42 and 27 years, respectively). In this analysis, we found that the oldest relatives had a significantly higher systolic blood pressure at rest and during dynamic muscle work ($p < 0.05$) and at psychological stress ($p < 0.01$), when compared to the controls of the corresponding age group.

ECG findings at rest and during dynamic exercise

Twelve relatives (6.2%) had ECT signs indicating left ventricular hypertrophy as compared to 3.0% in controls (n.s.). The T-wave amplitude in V_5 was significantly lower ($p < 0.01$) in relatives as compared to controls (mean difference 0.6 mm). During dynamic muscle work, 8 relatives had pathological changes of the T-wave from rest to work, according to the Minnesota code 12, but only one of the controls. The relatives and controls with these reported ECG changes at rest and during exercise did not differ from the other relatives or controls in blood pressure or heart rate reaction during or after the tests.

Invasively measured blood pressure and haemodynamics as well as arterial blood gases and lactate at rest, during static muscle work, cold pressure test, psychological stress and dynamic muscle work (Paper III)

Blood pressure and heart rate

This study started with a non-invasive measurement of blood pressure at rest. In a comparison between relatives (n = 26) and controls (n = 15) systolic blood pressure was significantly higher in relatives ($p < 0.05$). No significant difference was found between the groups in diastolic blood pressure or heart rate.

Invasively measured, the difference between relatives and controls in systolic blood pressure at rest decreased. Nevertheless, during the tests both systolic and diastolic blood pressures were higher in relatives as compared to controls except at cold pressure test and the highest load of dynamic muscle work, where the difference between the groups decreased. Heart rate did not differ in relatives and controls, either before, during or after the tests.

Haemodynamics

Cardiac index at rest was identical in relatives and controls (3.4 l/min/m^2). During dynamic muscle work, cardiac index rose less in relatives as compared to controls.

Peripheral vascular resistance was higher in relatives as compared to controls both at rest and during the tests. The difference to controls did, however, not reach statistical significance. Stroke index was generally lower in relatives except at static muscle work and at rest before cold pressure test. There was a significant, negative correlation between heart rate and stroke index during static ($r = -0.54$; $p < 0.01$) and dynamic muscle work ($r = -0.85$; $p < 0.001$) in relatives, but not in controls.

Blood gases and lactate

Arterial blood $p\text{CO}_2$ was lower in relatives as compared to controls, both at rest and during all procedures. The differences between the groups reached statistical significance at rest, during psychological stress and dynamic muscle work ($p < 0.05$). Blood standard bicarbonate was generally lower in relatives and pH and lactate were slightly higher in relatives as compared to controls. These differences between the groups did not, however, reach statistical significance.

Plasma volume and plasma volume distribution at rest and during static muscle work, cold pressure test, psychological stress and dynamic muscle work (Paper IV)

Total plasma volume (TPV)

TPV was measured in 35 relatives and 25 controls. TPV was significantly lower in relatives as compared to controls (16.5 and 18.4 ml/cm, respectively; $p < 0.001$). Total blood volume was significantly lower in relatives as compared to controls (27.3 and 30.2 ml/cm, respectively; $p < 0.01$). There was a significant, negative correlation in relatives between TPV and systolic blood pressure ($r = -0.38$; $p < 0.05$) and diastolic blood pressure ($r = -0.44$; $p < 0.05$) but not between TPV and heart rate. No correlations were found between TPV and blood pressure or heart rate in controls. There was no correlation between TPV, hematocrit or plasma albumin concentration, either in relatives or controls. Also when matching relatives and controls into two strictly normotensive groups, TPV was significantly lower in relatives as compared to controls (systolic blood pressure ≤ 140 mmHg, $p < 0.05$; diastolic blood pressure ≤ 80 mmHg, $p < 0.001$).

Central plasma volume (CPV)

Central plasma volume was identical in relatives ($n = 16$) and controls ($n = 13$). Since TPV was significantly lower in relatives, the ratio CPV/TPV was higher as compared to controls. The difference in CPV/TPV between the groups reached statistically significant levels at psychological stress test ($p < 0.05$) and dynamic muscle work ($p < 0.01$). The ratio CPV/TPV increased more in relatives from rest to submaximal dynamic work ($p < 0.001$) as compared to the increase in controls ($p < 0.05$). There were no correlations between CPV and blood

pressure heart rate, plasma albumin or hematocrit, either in relatives or in controls.

Plasma levels of catecholamines and plasma renin activity at rest, during static muscle work and cold pressure test, in male relatives and controls (Paper V)

Plasma catecholamines

Plasma norepinephrine (NE) was generally lower in relatives ($n = 23$) but at a statistically significant level only during the cold pressure test ($p < 0.05$). NE was significantly correlated to systolic blood pressure at rest in relatives ($r = 0.55$; $p < 0.05$) but not in controls ($n = 15$). No significant difference between the groups was found in the mean value of plasma epinephrine (E) either at rest or during the tests. There was a significant correlation in both groups between E and cardiac index both at rest and during the tests.

Plasma renin activity

No significant difference was found between relatives and controls in plasma renin activity. During cold pressure test plasma renin activity was found to be significantly correlated to cardiac index in relatives ($r = 0.53$; $p < 0.05$) but not in controls ($r = 0.49$; n.s.).

Venous volume and blood flow in the hand at rest and during a psychological stress test (Paper VI)

There was no difference in venous volume in the hand between relatives ($n = 19$) and controls ($n = 19$), either at rest or during or after the stress test. Hand blood flow was slightly higher in relatives as compared to controls both at rest and during the test. Vascular resistance increased significantly in relatives during psychological stress ($p < 0.05$) but not in controls. The time both for venous volume and blood flow to return to basal levels after psychological stress was slightly longer in relatives as compared to controls.

GENERAL DISCUSSION

MATERIAL AND METHODS

Representativity of the subgroups studied

The individuals in this study were all members of families in which at least one individual in two consecutive generations had suffered from EH. Only family members, who had no known hypertension and also were within 20-60 years of age, were invited. For practical reasons we limited the invitation to relatives living in the neighbourhood of Malmö. With this selection of the investigated relatives there seems to be little reason to believe that the 332 investigated relatives should not be a representative subsample of the total of 1075 that were traced.

The subgroups of relatives for the different subsequent studies were carefully checked so that they were representative of the whole population of relatives (169 males and 138 females), participating in the first investigation. The results from these comparisons are reported in each study.

All individuals from the first study (Paper I) were invited to further investigation of blood pressure and heart rate during different tests (Paper II). A total of 64% of the relatives accepted this invitation. Judging from the results of the first investigation (Paper I), there were no significant differences in age, sex, height, weight, blood pressure or heart rate between those relatives, who accepted the invitation to the second examination (Paper II), and those who did not. In studies III-VI, only the results from studies on male relatives and controls are reported. We have, however, also investigated women in all studies but not in nr VI. The number of women participating was too small for any conclusions. The possible influence of contraceptives and menstrual phases excluded the women of these small groups from the final report. In papers III-V we investigated only male relatives, who were relatives to hypertensive subjects in families, where the occurrence of hypertension was at least 50% among the family members. Thus, although those relatives were not entirely representative from a genetic point of view as compared to the whole group of males investigated (Paper I), there were no significant differences in age, height, weight, blood pressure or heart rate between those two groups at the first investigation. The aim of the later studies (Papers III-V)

was to find haemodynamic characteristics in individuals prone to later hypertension. The controls were recruited from hospital staff members, firemen and other volunteers, all without known EH in their families for at least two generations, here called "genetic controls". In Paper I, comparisons were also made to adequate age cohorts of the screened population from the Department of Preventive Medicine, ranging around 70% of all individuals of each age in Malmö.

Measurement of blood pressure and heart rate

All measurements of blood pressure and heart rate of relatives and genetic controls in Paper I were performed by the same nurse at the same time of the day, between 1 and 3 p.m. The controls in the first investigation (Paper I), which consisted of individuals from the screened population, were investigated by different nurses. When taking into consideration the great number of individuals investigated, biased measurements of blood pressure between different observators should have been equalized. In the subsequent studies (Papers II-IV) two different nurses measured blood pressure randomly, both in relatives and controls at the examinations. Systolic blood pressure and heart rate were found to decrease in relatives between the different investigations, while the diastolic blood pressure remained almost constant. The fact that the subjects were more accustomed to the investigators and to the procedures may have contributed to the lowering of systolic blood pressure and heart rate at repeated examinations. One should not disregard the fact, that the recordings of blood pressure in the first study were obtained at noon, while in the subsequent studies blood pressure and heart rate measurements were obtained in the morning. It is known that blood pressure and heart rate have a tendency to rise during the day (30). The controls in the different studies were not entirely the same in the different investigations. Some of them were investigated only in one study. The relatives were thus investigated two or more times and were accustomed to the tests while the controls were investigated for the first time. This could to some extent explain the lower differences in blood pressure and heart rate between relatives and controls found in Papers II-V as compared to Paper I.

RESULTS

Blood pressure and heart rate at rest and during the tests

Systolic blood pressure and heart rate at rest in relatives were significantly higher as compared to controls. No significant difference was found in diastolic blood pressure between the groups with the exception for one small group of females. In Papers II-V, where the relatives and controls were studied during different tests, we could confirm that the differences between the groups in blood pressure and heart rate found at rest were maintained during all tests except at maximal dynamic work and cold pressure test. These findings support the conclusion that the differences between the groups found at rest were not accidental but caused by an increased cardiac output and/or increased peripheral vascular resistance in relatives. The blood pressure rise during static and dynamic muscle work as well as during psychological stress and cold pressure test has been used both as a prognostic and diagnostic aid in borderline and EH individuals (21,22, 27). A recent study (12) reports that both normotensive relatives of hypertensive patients and borderline hypertensives responded with a higher diastolic blood pressure to psychological stress as compared to controls. In some studies on EH, the maximal blood pressure response to muscle work and psychological stress was found to be higher when compared to normotensives (9, 15, 28). The relatives investigated in this study had almost the same blood pressure and heart rate response as the controls during the tests. Since the change in blood pressure and heart rate was almost the same, except during maximal dynamic work and cold pressure test, the difference between the groups was maintained both at rest and during the tests. Also when we compared the highest and lowest quartile of systolic blood pressure at rest in relatives, we found almost the same blood pressure and heart rate response to the different stimuli.

Haemodynamics at rest and during the tests (Paper III)

The aim of the invasive haemodynamic study was to establish if the differences found in blood pressure between relatives and controls was due to an increased cardiac output and/or an increased peripheral vascular resistance.

In established EH the peripheral vascular resistance is found to be increased, cardiac output lower and stroke volume normal or decreased as compared to normotensives (4, 5, 39). During exercise, the difference to controls in cardiac output, peripheral vascular resistance and stroke volume is maintained or even increased (1, 46, 49).

Borderline hypertensives have in several studies been found to have a high cardiac output at rest but a normal peripheral vascular resistance. During exercise the differences in cardiac output to controls have been found to disappear (21, 22, 29, 38). Cardiac index at rest among the relatives in this study was equal to that of the controls. During the tests, the peripheral vascular resistance was constantly higher in relatives as compared to controls. The difference was, however, not statistically significant. Also when comparing cardiac index of normotensive controls from other studies (7) and that of the controls in this study, almost identical figures were found, indicating that our methods are fully comparable to the studies referred. Six of our investigated relatives could be classified as borderline hypertensives but their cardiac index did not differ from that found among the rest of the investigated relatives.

As in Paper II, systolic and diastolic blood pressures were higher in the relatives at all resting measurements as well as during static muscle work and psychological stress. In spite of the fact that the differences between relatives and controls in Paper III did not reach statistical significance, the constancy of the observed differences as well as the similarity to the findings in the previous papers, indicate that the differences observed are true.

There was no statistically significant difference between relatives and controls as regards cardiac index at any of the seven observations. Furthermore, and contrary to what was found for the blood pressure, cardiac index did not tend to differ between the groups. Peripheral vascular resistance was, however, systematically higher in relatives as compared to controls at all seven observations. In spite of the lack of statistically significant difference in the present study, the results indicate that the increased blood pressure among the relatives is caused more by an increased peripheral vascular resistance than by an increased cardiac output.

In a 10-year follow-up study on borderline hypertensives, Lund-Johansen (29) reported that only the individuals with a normal cardiac output and a slightly elevated peripheral vascular resistance at the first investigation had increased their blood pressure at the second examination. Subjects with elevated cardiac output in the first examination did not increase their blood pressure to the same extent 10 years later. A widely accepted hypothesis has been that essential hypertension starts with a hyperkinetic circulation, secondarily giving structural changes of the vessels (14). As discussed above, our results in Paper III favour an increased peripheral vascular resistance rather than an increased cardiac output in our relatives. Regarding the higher systolic blood pressure and heart rate found among the relatives in the first study (Paper I) we can, however, not exclude the presence of some degree of hyperkinetic circulation at that examination.

Plasma volume and its distribution during the tests

A decreased total plasma volume has been described in EH by several authors (20, 37, 45, 47, 55). Also in borderline hypertensives a decreased total plasma volume has been reported (23, 40). In this study (Paper IV) we could demonstrate that also completely normotensive members of hypertensive families had a significantly lower plasma and blood volume as compared to controls. It is not probable that the results and methods in our study differ from that of the other studies, since there is a good agreement between the plasma volume in our controls and the plasma volume of normotensives in other studies (7). Parving (33) reported that the transcapillary escape of albumin was increased in hypertensives, who also had a significantly decreased plasma volume as compared to normotensives. Both in established EH and borderline hypertension, the cardiopulmonary fraction of the total plasma and blood volume has been found to be increased, indicating a shift of plasma and blood volume from the peripheral to the cardiopulmonary capacitance bed (11, 13, 48). In Paper IV we observed a constantly increased ratio central/total plasma volume during all tests in relatives as compared to controls. At psychological stress and dynamic muscle work the difference to controls was statistically significant. The increase of the ratio from rest to 50W dynamic work was higher in relatives ($p < 0.001$) as compared to controls ($p < 0.05$).

There were two findings in relatives in Papers III and IV, which seemed to be of importance. Firstly, the constantly elevated peripheral vascular resistance, secondly, the increased ratio central/total plasma volume. A transcapillary escape of plasma, depending on the blood pressure as discussed by others (33, 45) could be one explanation, but hardly in this study (Paper IV), since we found a significantly decreased plasma volume even in strictly normotensive relatives as compared to blood pressure matched controls. Another possible explanation for the decreased total plasma volume but unchanged central plasma volume could be a reduced venous distensibility as demonstrated by Takeshita (44) in a study on borderline hypertensives. Caliva (10) demonstrated that the digital venous pressure and vascular resistance was higher in hypertensives vs. normotensives. For this reason we decided to study both capacitance and resistance vessels in the hand, which is an area dominated by skin tissue, with a plethysmographic method developed by Wood (56). In this study (Paper VI), we found that the peripheral vascular resistance tended to be even lower in the hand in relatives. The increase during stress was significantly higher in relatives as compared to controls. We found no increased contraction of the veins in the hand in relatives as compared to controls during the stress test. This indicates that the central redistribution of plasma found by other authors on borderline and EH subjects and also by us on normotensive relatives of hypertensive patients, must be caused by a venoconstriction in other territories than in the skin.

Human studies have been limited to studies of the venous capacity in the extremities. In animal studies on hypertensive rats, a decreased venous capacity has been found in the splanchnic veins (41). Since the visceral veins are known to contain around 20-25% of the circulating blood volume, an increased tone of the veins in this region could be responsible for the increased ratio central/total plasma volume. The total plasma volume might then have been adapted to this decreased space by central volume receptors. A reduced venous capacity could be induced by an increased sympathetic influence, either by increased levels of catecholamines and/or increased sensitivity to adrenergic stimuli. The relatives had constantly slightly lower plasma levels of norepinephrine as compared to controls. It is, however, not known if plasma levels of norepinephrine can be taken as an expression for the overall sympathetic activity at least because of lack of knowledge of the regional norepinephrine release or metabolism. Low plasma norepinephrine levels can,

however, certainly not be used as an argument for a high level of norepinephrine at the nerve terminal. One might thus speculate whether the relatives in this study had an increased sensitivity to catecholamines. In other studies performed on subgroups of the relatives in this study, we found an abnormally slow whole-body and cellular (erythrocytes) turn-over of ^{22}Na (18, 19). An abnormal and genetically derived high intracellular amount of sodium might give an increased ratio intracellular/extracellular water (3) and an increased ratio free/bound calcium, resulting in an increased tone of the smooth muscle (8).

In recent follow-up studies we found that the relatives investigated in the haemodynamic study and in the studies on plasma volume had an abnormally high intracellular amount of sodium in their erythrocytes as compared to controls. The metabolic findings in different subgroups of relatives reported: an abnormal sodium metabolism, a significant negative correlation between the intracellular contents of sodium and potassium (18, 19) and also a lower arterial blood pCO_2 , together with a decreased standard bicarbonate but almost equal pH in relatives as compared to controls - could be interpreted as an expression of a primary abnormality of the $\text{Na}^+\text{K}^+\text{ATPase}$ system in the former group. Since there is a high grade of structural similarity between the human $\text{Na}^+\text{K}^+\text{ATPase}$ and $\text{H}^+\text{K}^+\text{ATPase}$ enzyme complexes (26), an inherited abnormality in the intra- and extracellular distribution of protons might be possible. Another interesting finding, which could also be taken as an expression of high intracellular contents of sodium, was a significantly lower T-wave in V_5 in ECG of relatives as compared to controls (54) described in Paper II.

Differences between normotensive and age stratified subgroups of relatives and controls

It seemed desirable to investigate different parameters in strictly normotensive relatives as compared to controls. Thus in Paper II we subdivided the relatives into quartiles as regards the systolic blood pressure at rest. The relatives belonging to the lowest quartile of systolic blood pressure at rest were strictly normotensive, but had a similar increase in blood pressure increase during the tests as relatives belonging to the highest quartile of systolic blood pressure at rest. When matching relatives and controls into pairs with regard to age and to diastolic blood pressure at rest, we found that old relatives (≥ 40 years) had a higher systolic blood pressure at rest and

psychological stress as compared to their controls. When comparing relatives and controls of the same age but disregarding blood pressure at rest, we found that both systolic and diastolic blood pressures were significantly higher in the old group of relatives (≥ 40 years) as compared to the controls of corresponding age. No significant difference was found between relatives and controls belonging to the age group < 40 years. These results have been interpreted by us as a greater tendency in relatives to increase their blood pressure with increasing age as compared to controls.

In Paper III we formed subgroups of relatives and controls both concerning peripheral vascular resistance and blood pressure at rest. When we subdivided relatives into two groups, over and below the median of peripheral vascular resistance at rest, we found that the low arterial $p\text{CO}_2$ found in the whole group of relatives as compared to controls was also found in the half of the relatives with low peripheral vascular resistance, both at rest and during the tests, indicating that this mechanism is present in the normotensive stage. Plasma and blood volume (Paper IV) was significantly lower in normotensive relatives as compared to controls. Nevertheless, there was a weak but significant correlation between plasma volume and blood pressure in relatives, but not in controls. One could thus not disregard the possible connection between blood pressure and plasma volume at least not in individuals prone to a later hypertension.

Other studies have demonstrated that systolic blood pressure and heart rate at rest (32, 35), as well as plasma albumin concentration (43) have a high predictive value for a later rise in blood pressure. Obviously, a cross-sectional study like the present one cannot give any information about the prognostic implications of the observations made. We do not know which of the normotensive relatives will develop hypertension. For this reason, all participants in this study will be checked every fifth year in the future.

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Blood Pressure, Heart Rate and Plasma Albumin in Relatives of Hypertensive Patients

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ABSTRACT. A total of 1075 relatives of 106 individuals (proband) with treated essential hypertension and heredity for this disease have been investigated concerning the existence of hypertension. The prevalence of hypertension or hypertensive diseases was near 50 %. Of the deceased relatives, 77 % had a positive history for hypertension. Of the deceased relatives with cerebrovascular diseases, 52 % had expired before 65 years of age. We have examined 307 relatives of these probands. They had significantly higher systolic blood pressure, heart rate and serum albumin concentration than age- and sex-matched controls without heredity for hypertension and a screened population. Screening of relatives belonging to families with a high frequency of hypertension seems to have a potential practical value and may furthermore provide information about the etiology of the disease.

Key words: essential hypertension, familial aggregation, heart rate, serum albumin.

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Familial aggregation of elevated blood pressure (BP) is well known and is reported as early as in 1924 (15). Most studies on early hypertension have been performed in borderline or labile hypertensives, but the prevalence of later sustained hypertension in these individuals varies between study populations as reviewed by Julius and Schork (10). In most studies individuals with so-called borderline hypertension have a risk of developing later established hypertension about twice that of the normotensive population (10). A family history positive for essential hypertension is more prevalent among patients with borderline hypertension (9). Twin studies conclude that heredity is a very important factor in the development of essential hypertension (3). It has also been reported that individuals with elevated BP have an elevated concentration

of plasma albumin and hematocrit compared to matched normotensive controls (20).

The purpose of this study was to investigate whether there are any physical or biochemical characteristics in members of families with a known aggregation of essential hypertension differing from a screened population or controls without known heredity for hypertensive diseases. This report deals with the results of physical and biochemical investigations performed in relatives and the above mentioned control groups. More detailed analyses have been applied to subgroups of these relatives as well as to genetic controls and will be published elsewhere.

STUDY POPULATION

By investigation of consecutive records of hospitalized or out-patients during 1973–76, 106 investigated and treated patients (proband) with essential hypertension were selected for this study. All subjects entering the study should have at least one close family member (parents, siblings, offspring) with hypertension and/or cerebrovascular disease with onset before the age of 60 (18). Patients with manifest diabetes or secondary hypertension, such as known primary renal disease and/or endocrinological hypertension, were excluded. Requests regarding names and addresses of their off-spring and siblings and information of known hypertension or cerebrovascular disease among the latter and their parents were sent to all probands. They were also informed of future intended contact with those relatives and encouraged to report possible objections to this procedure.

All relatives aged 20–60 years without known treated hypertension living in the city of Malmö or its surroundings ($n=339$) were invited to an examination at the Department of Preventive Medicine. A total of 448 relatives were not included for either geographical reasons ($n=271$) or because of known treatment for hypertension ($n=177$). Of the 332 relatives who accepted the invitation and were examined, 236 (75 %) were first-degree relatives (parents, children or siblings), 21 % second-degree relatives (offspring to siblings) and 8 % third-degree relatives to the probands. We found that 25 relatives were on treatment for hypertension. The remaining 307 persons (169 males

Table I. Physiological and laboratory investigations in relatives, genetic controls and a screened population (Student's *t*-test)

Normal values are given in parentheses

	Relatives		Genetic controls	
	Age 20-39 ($\bar{X}$ 28±6)	Age 40-60 ($\bar{X}$ 47±5)	Age 20-39 ($\bar{X}$ 29±7)	Age 40-60 ($\bar{X}$ 46±6)
Males (n)	118	49	31	16
Physiological investigations				
Systolic BP (mmHg)	135.9±13.8	146.0±15.3	126.3±9.5***	123.9±9.6***
Diastolic BP (mmHg)	79.3±10.1	91.4±12.2	76.9±8.7	81.1±6.6**
Heart rate (beats/min)	74.8±11.4	75.0±9.9	65.3±10.6***	68.9±8.9
Height (cm)	178.9±6.0	175.1±5.8	176.6±7.3	172.9±7.1
Weight (kg)	76.2±11.8	76.2±9.3	76.8±11.9	74.3±11.0
Laboratory investigations				
Albumin (g/l) (40-52)	49.6±3.6	48.4±2.8	47.9±3.0*	44.0±2.1***
Hemoglobin (g/l) (131-163)	153.4±11.5	153.7±12.4	149.8±9.9	152.4±6.9
Hematocrit (%) (37-49)	44.4±2.7	44.3±2.6	43.4±2.6	43.6±1.8
Creatinine (μmol/l) (<115)	93±12	99±14	90±9	92±12
S-GT (μkat/l) (<1.0)	0.59±0.42	0.77±0.57	0.59±0.51	0.51±0.54
Females (n)	97	41	20	7
Physiological investigations				
Systolic BP (mmHg)	120.5±11.1	141.1±18.7	113.5±11.7*	123.6±12.1*
Diastolic BP (mmHg)	77.0±9.6	90.5±8.6	74.8±6.8	79.3±8.9**
Heart rate (beats/min)	76.4±9.8	78.0±11.5	67.7±9.5***	68.7±8.9
Height (cm)	164.9±5.9	163.8±6.6	164.9±7.0	164.5±5.9
Weight (kg)	58.8±9.5	63.3±6.6	60.6±9.0	63.3±11.8
Laboratory investigations				
Albumin (g/l) (40-52)	46.8±3.6	46.7±3.9	44.1±2.7**	41.8±2.6**
Hemoglobin (g/l) (115-147)	132.8±9.5	136.8±8.4	131.9±5.6	137.5±13.5
Hematocrit (%) (37-49)	39.4±3.3	40.8±3.4	38.5±1.9	40.5±4.3
Creatinine (μmol/l) (<115)	75±10	76±11	74±9	78±9
S-GT (μkat/l) (<1.0)	0.48±0.65	0.44±0.19	0.42±0.26	0.42±0.15

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

and 138 females) were invited to further investigations and examinations including laboratory tests. All but two relatives accepted.

Reference groups

The reference population for predicted BPs, pulse rates and laboratory investigations was selected among those screened at the Department of Preventive Medicine (12). This group consists of 2701 males from the cohorts born in 1927, 1938 and 1949 and of 2701 females from the cohorts born in 1931, 1938 and 1949.

We also compared the relatives with 74 normotensive volunteers thoroughly questioned about hypertensive diseases in their families. They had no known hereditary factor for hypertension and were included as a control group called genetic controls.

The relatives and controls of both sexes have been grouped as shown in Table I.

METHODS

The probands were not investigated further. BP and pulse measurements of the relatives and genetic controls were

recorded by the same nurse at the same time of the day, at 1-3 p.m., and in the screened population at 9-11 a.m. BP was measured in both arms with a mercury manometer after exactly 10 min rest in the supine position and in the right arm after 2 min standing. The highest of the two registrations after 10 min rest in the supine position was used. Cuffs of two sizes were used, 12×35 cm in normal-weight and 14×42 cm in obese persons. Disappearance of the Korotkoff's sound, phase V, was used as the diastolic BP; if it was heard all the way to zero, phase IV was used.

Height and weight of relatives and both control groups were recorded and laboratory investigations by routine methods of the Department of Clinical Chemistry, Malmö General Hospital, were carried out in the morning after 10 hours' fast.

Blood samples were taken for analyses of hemoglobin, hematocrit, ESR, serum electrolytes, creatinine, albumin, uric acid, glucose, cholesterol, triglycerides, and hepatic enzymes (S-ASAT, S-ALAT, S-ALP, S-GT), and 24-hour urinary excretion of sodium and potassium was determined.

Relatives and genetic controls were also examined with auscultation of heart and lungs, palpation of peripheral pulses to exclude signs of coarctation of the aorta, and

Screened population

Age 29	Age 48
533	1 232
124.5±11.0***	132.1±16.5***
80.5±8.5	88.7±10.3
65.2±9.1***	68.5±9.8***
177.8±7.0	176.7±6.6
74.6±10.7	77.7±11.6
46.9±2.5***	45.3±2.5***
149.6±10.0***	151.7±10.3
44.1±2.7	44.0±2.8
92±18	96±13
0.52±0.54	0.82±0.87
609	565
113.9±10.9***	121.2±16.4***
75.7±8.3	82.2±9.6***
68.6±9.1***	70.4±10.4***
166.0±6.1	163.6±5.9
59.1±9.5	65.2±11.7
44.3±2.6***	43.4±2.5***
132.9±8.6	133.5±9.5*
38.9±2.6	39.6±2.8*
73±12	75±12
0.35±0.32*	0.45±0.43

auscultation of the abdominal region to detect possible renal arterial stenosis. A medical history including information of all family members was obtained from all relatives examined. In this way we were able to obtain information from more relatives and to confirm anamnesic data from other members of the same family.

Relatives with history or record of treated hypertension with onset before 60 years of age are in this study said to have a positive history for hypertension. Relatives not having these criteria are said to have a negative history for hypertension.

Statistical standard methods were used. All values are given as $\bar{X} \pm \text{S.D.}$ unless otherwise stated. In calculations of body mass index (BMI, kg/m²), body surface was calculated according to du Bois.

RESULTS

Clinical Examination

The aim of the examination was to exclude secondary hypertensive mechanisms as far as possible. No sign of such disturbances was detected.

Prevalence of hypertension in the families studied

Twenty-five relatives had a negative initial history for hypertension but were nevertheless found to be treated with antihypertensive drugs at the time of examination. They are excluded in the presentations below. When adding them to the 10 examined relatives aged 30 years or less whose diastolic BP exceeded 95 mmHg and those 29 aged 30 years or more whose diastolic BP exceeded 100 mmHg at the time of examination, the prevalence of hypertension among the living members of all families was 39%.

Of the 288 relatives who had died (exclusively parents of the probands or their siblings), 221 (77%) had a positive history for hypertension. Of the deceased relatives with cerebrovascular diseases, 52% had expired before 65 years of age. When probands, deceased and living relatives in all families are taken together, 48% had hypertension.

Blood pressure and heart rate

As shown in Table I, the mean systolic BP was significantly higher in male and female relatives of both age groups than in the controls. Diastolic BP did not differ significantly between the youngest age groups. There was, however, a tendency to higher diastolic BP among the relatives in age group 40–60 compared to corresponding controls. The heart rate was significantly higher among both male and female relatives of both age groups compared to the screened population. The difference between the values of genetic controls was not significant in age group 40–60, possibly depending on the small number of individuals in this group.

Height and weight

There were no significant differences in height or weight between relatives and the two control groups of both sexes.

Correlation between heart rate and blood pressure

There was a small but significant correlation between heart rate and systolic BP both in male ($r=0.21$, $p<0.05$) and female relatives ($r=0.49$, $p<0.001$). In the genetic controls the correlation was significant only among males ($r=0.46$, $p<0.01$), not among females ($r=0.08$). Diastolic BP was also correlated to heart rate among female relatives ($r=0.40$, $p<0.001$) and male genetic controls

($r=0.49$, $p<0.01$), but not among male relatives ($r=0.04$) or female genetic controls ($r=0.01$).

Correlation between body mass index and blood pressure

There was no correlation between BMI and systolic or diastolic BP among the relatives. Among the male genetic controls there was a weak correlation in age group 20–39 (systolic BP $r=0.36$, $p<0.05$, diastolic BP $r=0.30$) but not among female genetic controls.

Laboratory Investigations

Albumin

Plasma albumin was significantly elevated in both age groups of relatives compared to both genetic controls and the screened population of corresponding ages.

When the relatives were subdivided into strictly normotensive individuals with BP $\leq 140/85$ (males $n=75$, S-albumin 49.2, females $n=85$, S-albumin 46.8) and individuals with BP $> 140/85$ (males $n=72$, S-albumin 49.4, females $n=38$, S-albumin 47.3), no significant difference in S-albumin was found in either sex between the subgroups.

Hemoglobin, hematocrit, creatinine and S-GT

There were no systematic differences between relatives and controls with regard to these parameters. An increase in mean S-GT with age was found among male relatives and males from the screened population, but not among male genetic controls or any of the female groups.

Other laboratory investigations

There were no significant differences between the above groups concerning the other laboratory investigations performed (ESR, serum electrolytes, uric acid, glucose, cholesterol, triglycerides, S-ASAT, S-ALAT, S-ALP or 24-hour urinary excretion of sodium and potassium).

Correlation between albumin and blood pressure

There was a significant correlation between systolic BP and albumin both among male and female relatives in age group 20–39 ($r=0.25$, $p<0.01$ and 0.33 , $p<0.001$, respectively). No significant correlation was found among the genetic controls of either sex.

There was no correlation between diastolic BP and albumin in relatives or genetic controls.

Correlation between S-GT and blood pressure

There was a significant correlation between S-GT and systolic BP among male and female relatives of both groups ($r=0.24$, $p<0.01$) and between S-GT and diastolic BP among male ($r=0.27$, $p<0.01$) and female relatives ($r=0.24$, $p<0.05$) but not among genetic controls.

Correlation between albumin and hematocrit

There was a significant correlation between albumin and hematocrit among male relatives ($r=0.25$, $p<0.001$) but not among females or any of the genetic controls.

DISCUSSION

The prevalence of hypertension in the families included in this study was 48%. Among the 67 deceased and 278 living relatives with a negative history for hypertension, several individuals may have had hypertension unknown to the living relatives or not revealed by the questionnaire. Among 332 examined relatives with a negative history for hypertension, 25 (8%) were on treatment for hypertension. For this reason 48% may be regarded as a minimal estimate of hypertension among the families studied. If we assume that 8% of relatives with a negative history for hypertension who were not examined also had hypertension, the prevalence would be 50% (Fig. 1).

Miall and Oldham (14) demonstrated a direct quantitative relationship between arterial BPs of the probands and their first-degree relatives. Obesity and essential hypertension also seem to be overrepresented among parents of children with essential hypertension (13). Hedstrand and Åberg (5) found in a three-year follow-up study of middle-aged men with borderline hypertension that a history of hypertension was more frequent (48%) among the parents of those who developed hypertension than of those who did not.

Blood pressure and heart rate

The systolic BP was significantly higher in both male and female relatives of all ages than in the controls. No significant difference was found in diastolic BP between male relatives and the screened

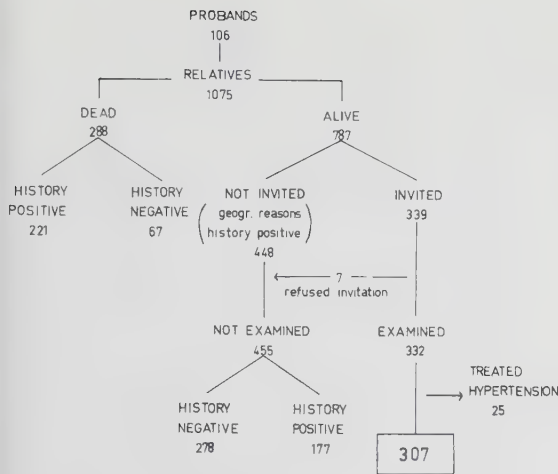


Fig. 1. The study population.

population. Among females the difference in diastolic BP was significant only in age group 40–60. The differences in both systolic and diastolic BP of the relatives increased with age. In the Framingham study (11), the initial systolic BP was a stronger predictor of coronary incidents than diastolic BP.

The heart rate was significantly elevated among both male and female relatives of all ages compared to the screened population. Elevated heart rate has been reported to correlate to a later development of essential hypertension (16, 17). Elevated systolic BP may be secondary to the increased heart rate and a significant correlation between these two parameters was found among the relatives.

However, all other factors constant, increased heart rate shortens diastole and should thus increase the diastolic BP more than the systolic BP. Theoretically there are two explanations of a selective increase in systolic BP: an elevated stroke volume ejected into an arterial system with normal compliance and capacity or a normal stroke volume ejected into a stiff arterial system.

Using the definition "borderline hypertension" regarding subjects with BPs varying between normal and slightly elevated, many studies indicate that these individuals have an increased heart rate, cardiac output and stroke volume, but a normal peripheral resistance (10). The differences found in this study could, for example, also be due to an occasionally increased anxiety, a hypothesis which is to some extent supported by subsequent follow-up of subgroups (6).

One suggested explanation of the elevated heart

rate could be increased sympathetic discharge of synaptic catecholamines or increased cardiac or vascular sensitivity to catecholamines. On the basis of plasma and urinary catecholamine levels, there are strongly divided opinions about whether an increased sympathetic discharge exists among subjects with mild or borderline hypertension. An increased vascular reactivity to catecholamines depending on the sodium balance has been shown in animal experimental hypertension reviewed by Haddy (4). In a study of normotensive sons of hypertensive patients, Doyle and Fraser (2) reported a significant increase in vascular resistance to noradrenaline infusion compared to controls without heredity for hypertension. The mechanism discussed by Haddy might be present among relatives in this study, since an abnormal, slow whole body turnover of ^{22}Na was found in a representative subgroup, as well as definite changes in ^{22}Na -uptake and increased sodium content in their erythrocytes (6).

Blood pressure and weight

We found no correlation between systolic BP and BMI in any group of relatives or genetic controls. Several population studies have shown a significant correlation between BP and weight or index of weight (1), but varying results concerning a later established hypertension have been presented in longitudinal studies (8). This might indicate that body weight alone is overestimated as a predictor of the development of essential hypertension.

Blood pressure and S-albumin

The significantly increased levels of albumin in all groups of relatives compared to both control groups is an interesting finding since this also has been found in established essential hypertension (20). In a 10-year follow-up study of middle-aged men it was found that the initial total serum protein level was positively correlated to the initial pressure level and the degree of subsequent rise (19).

The increased plasma albumin concentration could be an expression of hemoconcentration, i.e. decreased plasma volume, based on transcapillary escape of water into interstitial or intracellular compartments as shown in some animal experimental models (4). The significant correlation between systolic BP and albumin concentration in both male and female relatives in age group 20–39 as well as the correlation between albumin and hematocrit in

male relatives could indicate the presence of this mechanism. There was, however, no significant difference in S-albumin between relatives with BPs below or above 140/85 mmHg. The lack of correlation between albumin and hematocrit in females was expected because of a greater variation in hematocrit, probably caused by the influence of the menstrual cycle.

Blood pressure and S-GT

S-GT did not differ between relatives and controls. We found a significant correlation between S-GT and both systolic and diastolic BP among male and female relatives but not in the smaller group of genetic controls.

It was found in a previous study (7) that no less than 28.5% of individuals from a screened population of middle-aged males with a diastolic BP ≥ 105 mmHg had elevated S-GT levels ($\geq 1.44 \mu\text{kat/l}$). S-GT levels of this magnitude have also been found in association with excessive alcohol intake (12).

It remains to be seen whether elevated systolic BP, increased heart rate and increased plasma albumin, alone or in combination—more frequent among relatives than controls—are reliable predictors of development of essential hypertension.

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II

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THE EFFECT ON BLOOD PRESSURE, ECG AND HEART RATE OF PSYCHOLOGICAL STRESS, STATIC AND DYNAMIC MUSCLE WORK

A study on members of families with known aggregation of essential hypertension

Running headline: Heredity for hypertension and blood pressure during muscle work
and psychological stress

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Keywords: Hypertension, Genetics, Muscle Work, Psychological Stress Test.

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ABSTRACT

A total of 195 relatives of patients from families with essential hypertension in at least two generations have been examined in regard to blood pressure (BP) and heart rate (HR) during muscle work and psychological stress.

They were compared to controls without heredity for hypertension.

The differences between the groups in BP and HR at rest were maintained throughout all tests, but during heavy dynamic muscle work, the systolic blood pressure rose less in relatives than in controls.

When relatives and controls were divided into sub-groups, we found that blood pressure was more related to age in relatives than in controls, both at rest and during the provocation tests.

The differences in blood pressure between the groups could thus depend on a genetic factor with greater penetration with increasing age.

INTRODUCTION

In previous publications on hypertensive families (10) we reported an occurrence of known, treated or directly examined hypertension of about 50% among the members of the families studied.

In those families both men and women had a significantly higher systolic blood pressure and heart rate, compared to controls without heredity for hypertension as well as to representative samples of the population.

The diastolic blood pressure was, however, significantly higher only among female relatives older than 40 years.

The blood pressure reaction during static and dynamic muscular work as well as during psychological stress has been used as a prognostic and diagnostic aid in borderline and mild essential hypertension (6, 7, 8). The blood pressure response to these tests in borderline hypertensive individuals is usually similar to that of normotensives (11).

Most recent studies (3) report that both relatives of hypertensive patients and borderline hypertensives react with a higher diastolic blood pressure to psychological stress as compared to controls.

In some studies on established hypertensives the maximal blood pressure response to muscle work and psychological stress was found to be higher when compared to normotensives (1, 4, 8).

The aim of the present investigation was to study the degree of constancy of the raised blood pressures and heart rates in the members of hypertensive families both at rest and during various stress tests.

For this purpose a representative sub-group of relatives of patients from hypertensive families has been compared with age-matched normotensive controls without any known hypertension in the family.

MATERIAL AND METHODS

Material

The material consists of first (84%) and second degree relatives of 106 patients (probands) with essential hypertension (10). All probands had at least one other family member with essential hypertension and/or cerebrovascular disease with onset before the age of 60.

From the 106 probands we received anamnestic data of 288 dead and 787 living persons. All living relatives aged 20-60 years living in the city of Malmö or its surroundings were invited to examinations at the Department of Preventive Medicine. A total of 339 were invited, 332 accepted. Twenty-five of those relatives were found to be treated with antihypertensive drugs and for that reason were excluded from further examination.

The remaining untreated individuals ($n = 307$) were offered a further examination of blood pressure and heart rate during physical and psychological stress tests at the Department of Clinical Physiology. A total of 195 relatives accepted this invitation (114 males, mean age 35 ± 11.6 years, and 81 females, mean age 36 ± 11.8 years). The control group consisted of healthy normotensive volunteers (blood pressure $\leq 135/85$ mmHg), 44 males and 24 females, mean age 35 ± 9.5 and 37 ± 7.9 years, respectively. They were recruited from hospital staff members, fire-men and also randomly selected from different age cohorts screened at the Department of Preventive Medicine. All were examined in the same way as the relatives. They had had no known hypertension in their families for two generations.

Methods

The examination was performed in the morning (8 to 10 a.m.). All individuals had been requested to abstain from food and smoking for at least 8 hours prior to the investigation. After 10 minutes' rest in the supine position, blood pressure was measured in both arms. The disappearance of the Korotkoff's sounds was chosen to indicate the diastolic blood pressure. In those cases where this was not clearly defined, we used Korotkoff phase IV.

A 12-lead ECG (I, II, III, aVR, aVL, aVF, $V_1 - V_7$) was recorded in the conventional way both at rest and during the provocation tests. The paper speed at rest was 50 mm/s, during the provocations 10 mm/s, but the speed was altered to 50 mm/s every second minute when blood pressure was also measured. All electrocardiograms during and after the tests were interpreted according to the Minnesota code.

After each test the subject rested until blood pressure and heart rate were unchanged on two consecutive readings at two minutes' interval.

Static muscle work: The provocation tests started with a hand grip test. When we had found the maximal capacity for each subject, they rested until blood pressure and heart rate had gone down to basal levels. After that, the work was performed at 30% of the maximal capacity for 5 minutes in accordance with earlier studies in this field (2).

Psychological stress: For this part of the study we used a binary choice generator. In front of the patients there were two lamps which switched on spontaneously, one at a time. At each twinkling the patient was requested to press the corresponding button. The intervals between the twinklings were decreased every 15 second. The test was interrupted when the number of missed and incorrect pushes exceeded the correct ones.

Dynamic muscle work: This was performed with the patient sitting on a bicycle ergometer. The initial loads were 50 W for males and 35 W for females. With intervals of four minutes, these loads were increased to 100 and 145 W for men and to 65 and 130 W for women.

Standard statistical methods were used. For the comparison of groups Student's t-test was used.

RESULTS

The main results are given in Tables I and II and Figs. 1-4.

Unless otherwise stated, no significant differences were found.

There were no significant differences in age, height, weight, blood pressure or heart rate in either sex between relatives from the whole population investigated ($n = 307$) and the relatives who accepted to participate in this study ($n = 195$). At the second examination differences were found in systolic blood pressure as can be seen in Table I.

INITIAL RESTING PERIOD (Table I)

Systolic blood pressure (SBP)

The relatives had significantly higher SBP as compared to controls (male relatives 135 mmHg, controls 125 mmHg; female relatives 124 mmHg, controls 114 mmHg; $P < 0.001$ and $P < 0.01$, respectively).

Diastolic blood pressure (DBP)

Both among male and female relatives DBP was significantly higher as compared to controls (male relatives 84 mmHg, controls 79 mmHg; female relatives 79 mmHg, controls 74 mmHg; $P < 0.01$ and $P < 0.05$, respectively).

Heart rate (HR)

There was a tendency towards higher HR both among male (72/min) and female (72/min) relatives as compared to controls (70 and 68/min, respectively). These differences did not, however, reach statistical significance.

Table I. Comparison between the whole population of relatives (first investigation), the sub-group in this investigation on both occasions and the controls. M $\pm$ SD and results of Student's t-test. $p < 0.001 = ***$, $p < 0.01 = **$, $p < 0.05 = *$

	Age		Height		Weight		Systolic blood pressure		Diastolic blood pressure		Heart rate	
	M	F	M	F	M	F	M	F	M	F	M	F
All relatives	35	35	178	164	76	60	139	127	83	81	75	77
(first investigation)	$\pm 12.7 \pm 12.4$	$\pm 6.3 \pm 6.3$	$\pm 11.2 \pm 9.9$	$\pm 14.7 \pm 17.0$	$\pm 12.3 \pm 11.4$	$\pm 11.0 \pm 10.5$						
169 men, 138 women												
Present sub-group	35	36	178	165	76	60	141	126	85	81	75	75
(first investigation)	$\pm 11.6 \pm 11.8$	$\pm 6.1 \pm 5.9$	$\pm 10.8 \pm 9.7$	$\pm 15.5 \pm 16.5$	$\pm 11.2 \pm 10.2$	$\pm 11.6 \pm 11.2$						
114 men, 81 women												
Present sub-group	35	36	178	165	76	60	135	124	84	79	72	72
(this investigation)	$\pm 11.6 \pm 11.8$	$\pm 6.1 \pm 5.9$	$\pm 10.8 \pm 9.7$	$\pm 15.1 \pm 15.4$	$\pm 10.9 \pm 9.6$	$\pm 13.9 \pm 11.0$						
114 men, 81 women												
Controls	35	37	176	165	78	62	125	114	79	74	70	68
(this investigation)	$\pm 9.5 \pm 7.9$	$\pm 7.0 \pm 6.8$	$\pm 11.6 \pm 10.3$	$\pm 9.4 \pm 12.0$	$\pm 6.7 \pm 8.1$	$\pm 11.6 \pm 9.8$						
44 men, 24 women												

ALL RESTING PERIODS

In both relatives and controls no significant difference was found when comparing SBP, DBP and HR from the initial resting period with corresponding variables at the following resting periods. When adding all resting periods in each group, SBP and DBP - but not HR (n.s.) - in male relatives was found to be significantly higher when compared to controls ($P < 0.001$).

In females all variables were significantly higher in relatives as compared to controls (SBP $P < 0.001$; DBP $P < 0.001$; HR $P < 0.01$).

Static muscle work and psychological stress (Figs. 1-4)

During static muscle work and psychological stress the differences between relatives and controls in SBP, DBP and HR found at rest were strictly maintained both during the tests and at rest after the tests.

The fall in SBP 2 minutes after psychological stress was 6 mmHg in male relatives and 3 mmHg in controls ($P < 0.05$).

Dynamic muscle work (Figs. 1-4)

The differences in blood pressure between relatives and controls were maintained up to maximal work. After that, the differences between the groups decreased.

After working 4 minutes at 100 W, the female relatives increased their HR by 8 beats per minute more than the controls. This difference in heart rate reaction was statistically significant ($P < 0.01$).

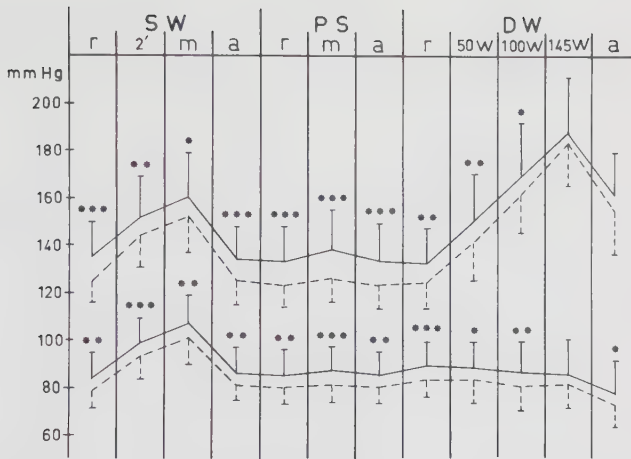


Fig. 1. Systolic and diastolic blood pressure in 114 male relatives (—) and 44 male controls (---) during static muscle work (SW), psychological stress (PS) and dynamic muscle work (DW) at rest before work (r), at 2 minutes' work (2'), at maximal work (m) and after work and psychological stress, respectively, (a). $P < 0.001 = ***$, $P < 0.01 = **$, $P < 0.05 = *$.

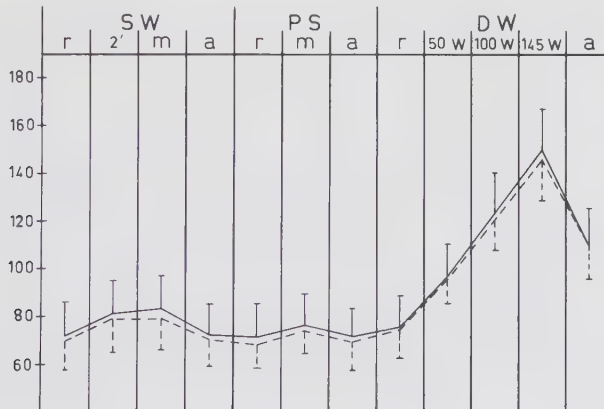


Fig. 2. Heart rate in 114 male relatives (—) and 44 male controls (---) during static muscle work (SW), psychological stress (PS) and dynamic muscle work (DW) at rest before work (r), at 2 minutes' work (2'), at maximal work (m) and after work and psychological stress, respectively, (a).

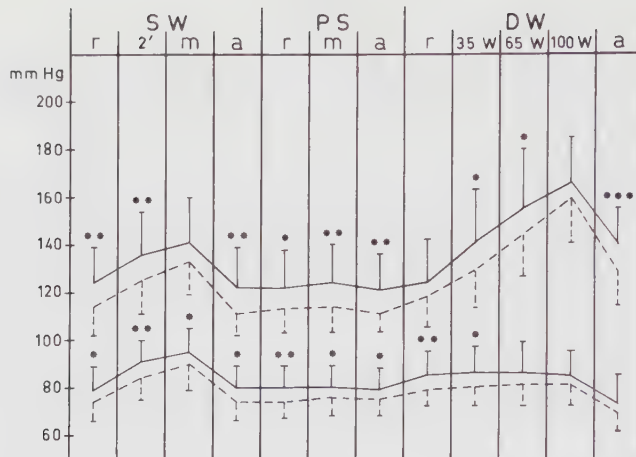


Fig. 3. Systolic and diastolic blood pressure in 81 female relatives (—) and 24 female controls (---) during static muscle work (SW), psychological stress (PS) and dynamic muscle work (DW) at rest before work (r), at 2 minutes' work (2'), at maximal work (m) and after work and psychological stress, respectively, (a).

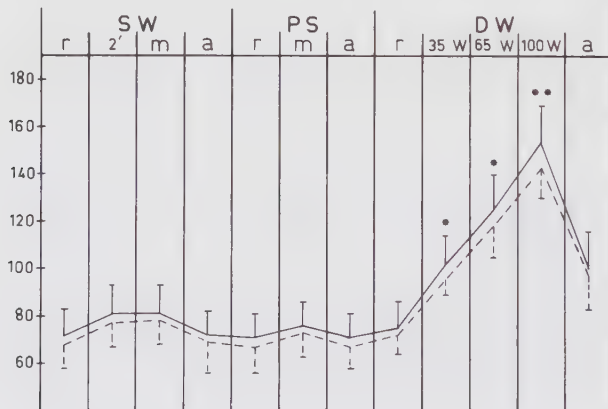


Fig. 4. Heart rate in 81 female relatives (—) and 24 female controls (---) during static muscle work (SW), psychological stress (PS) and dynamic muscle work (DW) at rest before work (r), at 2 minutes' work (2'), at maximal work (m) and after work and psychological stress, respectively, (a).

$P < 0.001 = ***$, $P < 0.01 = **$, $P < 0.05 = *$.

ECG FINDINGSAt rest

All relatives and controls had sinus rhythm. Twelve relatives (6.2%) showed signs of left ventricular hypertrophy, as compared to 3.0% among the controls. The difference was not, however, statistically significant. Seven relatives had minimal T-wave negativity in $V_4 - V_7$, none of the controls. The T-wave amplitude in V_5 was significantly lower ($P < 0.01$) in the relatives (0.6 mm).

Dynamic muscle work

A total of 8 relatives had pathological changes of the T-wave from rest to work, according to the Minnesota-code 12, but only one of the controls.

Comparison between age and blood pressure matched sub-groups of male relatives and controls

Since female relatives and controls were too few to make an exact age and blood pressure matching possible, this subdivision has been limited to male relatives and controls.

Male relatives and controls of the two age groups < 40 years and ≥ 40 years were compared. Mean age in age group < 40 years in relatives was 29 ± 5.4 years (median age 29 years) ($n = 80$), in controls 30 ± 5.4 years (median age 29) ($n = 25$).

When comparing relatives of the youngest age group with corresponding controls, no significant difference in SBP (131 and 128 mmHg, respectively) was found either at rest, or during the tests.

In the age group ≥ 40 years, the mean age of the relatives was 49 ± 7.4 years (median age 47) ($n = 34$), of the controls 47 ± 3.8 (median age 48) ($n = 19$). We found that SBP at rest was significantly higher among the relatives belonging to the oldest group as compared to corresponding controls (141 and 122 mmHg, respectively; $P < 0.001$).

These differences in SBP were maintained during all tests except at maximal dynamic work where the difference between the groups decreased (14.8 mmHg; $P < 0.05$). At 2 minutes after work the difference between the groups was again significant (22.6 mmHg; $P < 0.01$).

When comparing SBP of the oldest and the youngest group of relatives we found a significant difference between the groups at rest (141 and 131 mmHg, respectively; $P < 0.001$). During the tests these differences were maintained except at 2 minutes after static and dynamic muscle work, when they decreased.

When the same comparison was made between the age groups in the controls no significant difference was found in SBP either at rest or during the tests. Two minutes after dynamic work we found that the controls in the youngest group had a significantly higher ($P < 0.01$) SBP as compared to the oldest group (160 and 143 mmHg, respectively).

In a comparison of DBP between these age groups of relatives and controls the results were as follows:

DBP was significantly higher among the oldest group of relatives as compared to corresponding controls (89 and 79 mmHg, respectively; $P < 0.01$). These differences were maintained during the tests. The difference in DBP between the youngest group of relatives and the corresponding group among the controls was not significant (81 and 79 mmHg, respectively) either at rest or during the tests.

Finally, when comparing DBP between relatives of these age groups, it was found that there was a significant difference between the groups at rest (≥ 40 years 89 mmHg; < 40 years 81 mmHg; $P < 0.001$).

These differences were maintained at psychological stress ($P < 0.01$) and dynamic muscle work ($P < 0.001$).

In the controls no difference in DBP was found either at rest (79 mmHg in both groups) or during the tests.

HR was not statistically different, either at rest or during the different tests in comparisons between or within the above-mentioned age groups of relatives and controls.

To make it possible to compare the reactions due to the various pressure stimuli and to disregard the effects of age and systolic and diastolic blood pressures, we arranged two series with exactly matched relatives and controls.

When we matched according to systolic blood pressure and age, the result was a series of 25 pairs with a mean systolic blood pressure of 126 mmHg and a mean age of 33 years, ranging from 110 to 140 mmHg. The rise in SBP, DBP and HR caused by the stimuli was almost identical in relatives and controls.

We then divided this series into two halves according to age - older and younger relatives (mean age 40 and 27 years, respectively) and older and younger controls (mean age 39 and 26 years, respectively).

When comparing these groups, we found no significant difference between the groups either at rest or during the tests.

The same procedure was repeated when we matched according to diastolic blood pressure at rest, where we had 32 pairs with a mean age of 34 years and a mean diastolic blood pressure of 80 mmHg. No differences in blood pressure or heart rate were found between relatives and controls.

Here too, we arranged two series according to age, relatives: mean age 39 and 27 years, respectively, controls: mean age 42 and 27, respectively.

In this latter analysis relatives in the oldest group had a significantly higher SBP at rest and dynamic muscle work ($P < 0.05$) and at psychological stress ($P < 0.01$) when compared to the controls of the corresponding age group.

Table II. Comparison between the lowest and highest quartiles of systolic blood pressure at rest, during static muscle work (SW), psychological stress (PS), dynamic muscle work (DW) and after dynamic muscle work in male and female relatives. Means and results of Student's t-test are given.
 $P < 0.001 = ***$, $P < 0.01 = **$, $P < 0.05 = *$.

	Males, n = 114		Females, n = 81	
	Lowest	Highest	Lowest	Highest
Age	32.5 **	43.3	28.8 ***	49.5
Body mass index	38.1 **	40.2	34.8 **	37.2
Albumin	48.5	50.0	46.2 *	48.4
Hematocrit	43.8	45.0	38.0 **	40.8
First degree relative	17	22	11	17
<u>SW (rest)</u>				
Systolic blood pressure	116.4	155.0	108.2	146.1
Diastolic blood pressure	75.6 ***	92.6	69.7 ***	90.0
Heart rate	63.9 ***	78.4	71.6	75.9
<u>SW (maximal work)</u>				
Systolic blood pressure	144.4 ***	179.7	127.0 ***	165.0
Diastolic blood pressure	101.0 ***	114.9	90.5 ***	103.2
Heart rate	75.4 ***	89.6	78.9	83.8
<u>PS (maximal)</u>				
Systolic blood pressure	120.6 ***	159.0	109.8 ***	146.9
Diastolic blood pressure	79.6 ***	95.4	71.3 ***	91.6
Heart rate	68.0 ***	84.2	75.0	77.9
<u>DW 4' (145W for men and 100W for women)</u>				
Systolic blood pressure	169.2 ***	213.0	155.8 ***	193.7
Diastolic blood pressure	77.8 ***	99.7	80.8 ***	96.1
Heart rate	144.1	151.5	157.4	155.3
<u>DW 2' after</u>				
Systolic blood pressure	142.6 ***	174.8	130.2 ***	154.2
Diastolic blood pressure	66.3 ***	90.0	61.3 ***	85.0
Heart rate	105.3	108.9	100.1	98.0

Relatives and controls sub-divided into quartiles (Table II)

Relatives and controls of both sexes were sub-divided into quartiles based on SBP at rest.

In this analysis it was found that the quartile of male and female relatives with the highest SBP (quartile IV) was significantly older and had a higher body mass index (BMI) when compared to the quartile with the lowest SBP (quartile I).

DBP at rest was also significantly higher in the former group and the significant differences between the groups in SBP and DBP found at rest were also maintained during and after all tests. The significant differences in HR between the quartiles were maintained only during the tests, but the differences at rest after dynamic muscle work grew less.

There was a tendency towards a higher plasma albumin and hematocrit in the relatives of quartile IV, but as compared to quartile I the difference was only statistically significant among the females.

In the controls there were no significant differences between quartile I and IV as regards age, BMI, albumin or hematocrit.

In the male controls there were no significant differences between the quartiles in DBP or HR during or after the tests.

In the female controls DBP was significantly higher in quartile IV during and after each test, but there was no significant difference in HR between quartile I and IV.

When the relatives were sub-divided according to degree of relationship to the proband we found that first degree relatives were over-represented in quartile IV, both in males and females.

The blood pressure and HR responses to muscle work and stress tests were practically equal in the quartiles both in relatives and controls.

DISCUSSION

In our previous examination of relatives of patients from hypertensive families (10) we found that the average systolic blood pressure, heart rate and plasma albumin were higher among relatives of hypertensive patients of both sexes and all ages as compared to controls. In the present study the members of hypertensive families had somewhat lower blood pressures and heart rates than in the previous investigation (10).

It may be seen in Table I that the present sub-group of relatives did not differ from the whole group of relatives at the initial investigation with regard to blood pressures, heart rate, age, height or weight.

In these respects the sub-groups therefore seem representative of the whole group of relatives from hypertensive families.

The lower blood pressures and heart rates in the present study may be due to the fact that these recordings were made in the morning, whereas blood pressures and heart rates in the previous study (10) were recorded at noon. It is known (9) that blood pressure and heart rate tend to rise during the day. The fact that the subjects were now more accustomed to the procedure of the investigation may also have contributed to the lowering of blood pressures and heart rates.

In spite of the lower blood pressures and heart rates in the present investigation, the relatives of hypertensive patients still had higher blood pressures than controls. In fact, the differences between relatives and controls as regards systolic and diastolic blood pressures (Figs. 1 and 3) remained constant during nearly the whole period of examination in the present study. Only during dynamic exercise did the systolic blood pressure of the controls approach that of the group of relatives. During dynamic exercise systolic blood pressure thus rose less among the relatives than among the controls.

This may indicate that cardiac output increased less among the relatives than among the controls during dynamic exercise. An alternative explanation could be that the peripheral resistance decreased more during exercise in the relatives.

Although there was no statistically significant difference between relatives and controls at the start of the present study, heart rate was higher in relatives than among controls at most of the observation periods presented in Figs. 2 and 4.

The relatives as a group differed from the controls as regards systolic and diastolic blood pressure, but the standard deviations presented in Figs. 1 and 3 showed that there was a considerable overlapping between the two groups.

By dividing relatives and controls into sub-groups we found that blood pressure was more related to age in the relatives than in the controls, both at rest and during the provocation tests. When strictly matching age and SBP at rest in relatives and controls, no significant difference appeared between the groups during or after the tests. But when forming sub-groups according to age, we found that the oldest relatives had a higher blood pressure increase as compared to matching controls.

Obviously, many of the relatives had blood pressures entirely within the range of the controls. For this reason, it seemed desirable to analyze in what way the relatives with the highest blood pressures differed from those with the lowest blood pressures.

The relatives were thus divided into quartiles as regards systolic blood pressure at rest (Table II).

In that analysis it was found that the quartile of male and female relatives with the highest SBP were significantly older and also had a higher DBP and HR at rest and during all tests as compared to the quartile with the lowest SBP.

In the male controls no difference was found between the quartiles in DBP or heart rate during or after the tests. The female controls were, however, too few to allow any conclusions about differences in the variables of the quartiles.

There was also a considerable difference in age between female relatives of quartile I and IV (21 years) as compared to the female controls of each quartile (6 years).

When comparing the male controls of quartile I, aged 36 years, selected because of absence of hypertension among their family members, with the relatives in quartile IV in this study, 43 years of age, it was found that the blood pressure response was practically identical in the two groups.

The increased hematocrit and albumin concentrations found among the relatives in quartile IV is an interesting finding which agrees with those of our earlier investigation of the whole population of relatives (10). This might be explained by a hemoconcentration based on transcapillary escape of water into interstitial or intracellular compartments as shown in some animal and experimental models (5).

In a follow-up study (12) both the initial serum protein level and indices of weight have been found to be positively correlated to the initial blood pressure level and the degree of subsequent rise.

As demonstrated in an earlier study (10), BP was higher among relatives of all ages when compared to age matched controls, but the differences were greater at ages ≥ 40 years.

When sub-dividing male relatives and controls in groups ≥ 40 years of age and < 40 years of age, both SBP and DBP were also found to be higher in relatives ≥ 40 years as compared to younger relatives as well as to controls. No such difference was seen among the controls.

In a strictly age and BP matched group of relatives and controls no differences were found either at rest or during the tests, but in sub-groups divided by age the increase in BP was higher in older relatives as compared to controls.

The differences in BP between relatives and controls in the sub-groups and quartiles could thus be due to a genetic factor with greater penetration at ages ≥ 40 years.

The differences in BP and HR between members of hypertensive families and controls observed here were also found in our previous study. In that study (10) HR did not increase to the same extent with increasing age as it was found to do in quartile IV in this study. It thus seems as if HR was closer related to BP than to age.

This study has demonstrated that the differences in BP and HR at rest between relatives of hypertensive patients and controls remained fairly constant before, during and after static work test and a psychological stress test. Only during maximal dynamic work did the differences between the groups disappear. When matching the groups strictly by age, we also found that the blood pressure response to the tests was higher in older relatives as compared to their controls. The

observation that the relatives with the highest blood pressure also had the highest heart rate might indicate a "hyperkinetic" circulation in the members of hypertensive families.

In order to investigate whether the increased blood pressure is due to hyperkinetic circulation or to increased peripheral resistance it will, however, be necessary to measure cardiac output in a representative sub-group of members of hypertensive families.

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III

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BLOOD PRESSURE, CARDIAC OUTPUT AND SYSTEMIC VASCULAR RESISTANCE DURING
REST, MUSCLE WORK, COLD PRESSURE TEST AND PSYCHOLOGICAL STRESS

A study on male offspring from families with at least two generations
suffering from essential hypertension

Running headline: Heredity for hypertension and haemodynamics during muscle
work, psychological stress and cold pressure test

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ABSTRACT

Haemodynamic changes in the early phases of hypertensive diseases have mainly been described in so-called "borderline hypertensives". In those individuals, cardiac output has mostly been found to be elevated, but the peripheral vascular resistance normal. In this study on the offspring of hypertensive individuals, cardiac output and intravascular pressures were measured during rest, muscular work, psychological stress and cold pressure test.

The offspring had higher blood pressures at rest, during static muscle work and psychological stress.

The interesting finding in this group of individuals, selected not for labile blood pressure but for heredity for hypertension, was not an increased cardiac output, but an increased peripheral vascular resistance, both at rest and during the procedures.

Arterial blood $p\text{CO}_2$ in offspring was significantly lower as compared to controls, at rest, during psychological stress and dynamic muscle work. Possible mechanisms behind this finding are discussed.

INTRODUCTION

In a study on hypertensive families, we reported an occurrence of hypertension of about 50% among the 1186 members of the 106 families studied. From those families (307 individuals studied) both men and women had a significantly higher systolic blood pressure, heart rate and plasma albumin concentration compared to controls without heredity for hypertension as well as to representative samples of a screened population (22). In a study of a subsample of these relatives, we found that the difference in blood pressure between relatives and controls remained during different tests, but that this difference decreased during heavy dynamic muscle work (23). The increased heart rate might indicate the existence of a hyperkinetic circulation, which has been described in so-called "borderline hypertension" (14).

In view of these findings, it was decided to investigate whether the higher blood pressure among the relatives was due to a hyperkinetic circulation or to an increased peripheral vascular resistance or a combination of both. It was thus necessary to investigate the haemodynamics (cardiac output, stroke volume and peripheral vascular resistance) by invasive measurements in a representative subgroup of these relatives.

MATERIAL AND METHODS

Material

The offspring in this study were all selected from the earlier reported investigation on 106 families with at least two generations suffering from hypertensive diseases (22). A total of 169 males under the age of 60 years were investigated in that study. We found that 74 males were the offspring of hypertensive individuals in families, where the occurrence of hypertension was at least 50% among the family members.

The purpose was to select one male individual only from each family and in those families where more than one male offspring had been investigated in the previous study, a random selection was made of one of these for this invasive investigation. Five offspring refused to participate, a total of 26 individuals remained. The controls were age-matched normotensive volunteers with no known hypertension in their families for at least two generations. The subjects were all informed of the nature and purpose of the study and a voluntary consent was obtained.

Table I shows blood pressure (BP), heart rate (HR), age, height and weight in the population from which the offspring in this study were selected, as well as these figures from the previous non-invasive studies, here called the second investigation (23). Only three offspring in the present study had a systolic blood pressure exceeding 150 mmHg after 10 minutes rest in the supine position (155, 155 and 181 mmHg, respectively). Six offspring had a diastolic blood pressure exceeding 90 mmHg (95, 95, 95, 100, 105 and 105 mmHg, respectively). All controls except one had a blood pressure not exceeding 150/90. In this individual, the diastolic blood pressure was 95 mmHg.

Methods

The studies always started in the morning, at 8 a.m. and usually continued until noon. The individuals had been instructed to abstain from food and smoking for at least 8 hours before the investigation. After 10 minutes rest in the supine position, blood pressure and heart rate were measured. Before each procedure, the subjects were carefully instructed about all the tests, which followed the same order throughout.

Without previous anesthesia a venous polyethylene catheter (PE 160) was inserted percutaneously into an antecubital vein. During this insertion, blood pressure and heart rate were measured in the other arm. The tip of the catheter was placed in the right atrium under X-ray control. In local anesthesia, another polyethylene catheter of the same size was inserted percutaneously into the brachial artery. The tip of this catheter was placed in the axillary region.

Cardiac output (CO, l/min) was determined by a dye dilution technique, using bromsulphthalein as the indicator (8, 31). Cardiac index (CI) was determined as CO/body area ($l/min/m^2$). Mean arterial pressure (MAP) was obtained by electrical integration over a period including at least two respiratory cycles of the pressure curves. HR was obtained from ECG during the same time. The peripheral vascular resistance (PRI) was calculated from MAP/CI (units). Analyses for arterial blood gases (kPa), pH and lactate (mmol/l) were performed with procedures routinely used at the Department of Clinical Physiology (4, 13, 28). After each period the individuals rested until BP and HR reached the same levels as before the procedure; these were called basal levels.

"Pain stimulus"

The pain caused by the insertion of the needle for the venous catheter was called "pain stimulus". The aim was to find out if this stimulus could change the basal values of BP and HR obtained in the resting supine position (R) in a different way in relatives and controls.

Static muscle work

This was performed as a hand grip test. When the maximal capacity for each individual had been found, the static work was performed at 30% of the maximal capacity during 5 minutes. After 2 minutes, CO and intravascular pressures were determined.

Cold pressure test

In addition to the basal measurements of heart rate and blood pressure prior to this procedure, CO was determined. The test was then performed with one hand kept in ice-water up to the wrist. Injection for CO started again after 30 seconds and after that the intra-arterial blood pressure was measured. The total duration of the cold pressure test carried out in this way was 2 1/2 minutes.

Psychological stress

For this part a binary choice generator was used. In front of the individuals there were two coloured lamps (red and green), which switched on spontaneously one at a time. At each twinkling, the patient was requested to press the corresponding button. The intervals between the twinklings were decreased every 15th second. When the number of missed and incorrect reactions exceeded the correct ones, CO and intravascular pressures were measured, usually after 5-7 minutes.

Dynamic muscle work

This test was performed in the supine position with a bicycle ergometer. The load started at 50W for males and 35W for females. After four minutes the load was increased to 100 and after another four to 145W in males, the corresponding loads were 65 and 100W in females. The work was stopped when exhaustion was reached. After 2 minutes at 50 and 145W in men, and 35 and 100W in women, CO and intravascular pressures were determined.

Statistical methods

Standard statistical methods were used (Student's t-test) and the results presented in $\bar{X} \pm 1$ SD. We also tested the results with a variance test, but this did not change the significance of the results.

Representativity and comparability between the groups (Table I)

The present subgroup of relatives, selected for this study, differed from all male relatives of the first investigation by being selected from the families with the highest occurrence of hypertension. The present subgroup did not, however, differ from all male relatives earlier investigated as regards BP, HR, height, weight or age. The reproducibility of blood pressure was fairly good between the three occasions, when the offspring were investigated. There was, however, a significant decrease in heart rate from the first to the third investigation (6/min; $p < 0.05$). There were no significant differences between offspring and controls in body height, weight or age.

RESULTS

The results are summarized in tables I-II and figs. 1-4. Unless otherwise stated, no significant differences were found.

Non-invasively

At rest SBP was significantly higher in offspring compared to controls ($p < 0.05$). No significant difference between the groups was found for DBP or HR. During pain stimulus there was no difference in the change of SBP, DBP or HR between offspring and controls.

Invasively

At the invasive study, offspring and controls rested for five periods during which BP and HR were measured. No significant differences were found between the different resting periods within the groups. When the mean value

Table I. Systolic and diastolic blood pressure, heart rate, age, height and weight. Comparison is made between all male relatives at the first investigation and the subgroups at the different investigations.

$p < 0.05 = *$

	n	SBP	DBP	HR	Age	Height	Weight
All male relatives at the first investigation	169	139 ± 14.7	83 ± 12.3	75 ± 11.0	35 ± 12.7	178 ± 6.3	76 ± 11.2
The present subgroup at the first investigation	26	143 ± 14.5	87 ± 11.9	76 ± 10.2	35 ± 9.9	177 ± 6.3	76 ± 10.1
The present subgroup at the second investigation	21	136 ± 10.7	86 ± 9.3	74 ± 13.1			
The present subgroup at this investigation	26	137 ± 15.5	84 ± 11.6	70 ± 10.3 *			
Genetic controls at this investigation	15	127 ± 11.1 *	79 ± 9.2	69 ± 8.2	33 ± 9.3	177 ± 6.0	80 ± 13.8

of all SBP and DBP during the resting periods were calculated, we found that these parameters were significantly ($p < 0.05$) higher in offspring as compared to controls. No significant difference was found in HR. The haemodynamic parameters were measured twice at rest and after the same calculation no significant difference was found between these measurements, either in or between offspring and controls.

Blood pressure and heart rate during the tests

The change in SBP and DBP during static muscle work and psychological stress did not differ between offspring and controls. During cold pressure test and dynamic muscle work, the difference between offspring and controls decreased (Fig. 1). The small difference in HR between offspring and controls at rest (1-2/min) remained during all the procedures. At 2 minutes after dynamic muscle work, however, the mean HR was significantly higher in offspring, and the difference to controls became significant (113.6 and 100.7/min; $p < 0.01$).

CI, SI and PRI during the procedures

There was a tendency towards a smaller increase in CI (Fig. 2) and SI (Fig. 3) among offspring at dynamic muscle work as compared to controls. PRI (Fig. 4) was higher among offspring during all procedures. These differences to controls did not, however, reach statistical significance.

Blood gas analyses and lactate

$p\text{CO}_2$ was lower among offspring as compared to controls during all procedures (Table II). At rest before cold pressure test, at psychological stress and during heavy dynamic muscular work, the difference to controls reached statistical significance ($p < 0.05$). Standard bicarbonate was generally lower and pH only slightly higher in offspring than in controls during all procedures, but no significant differences were found between the groups. Lactate was slightly higher among offspring at dynamic muscle work 145W and at 2 minutes after work (4.6 and 5.9 mmol/l) as compared to controls (3.7 and

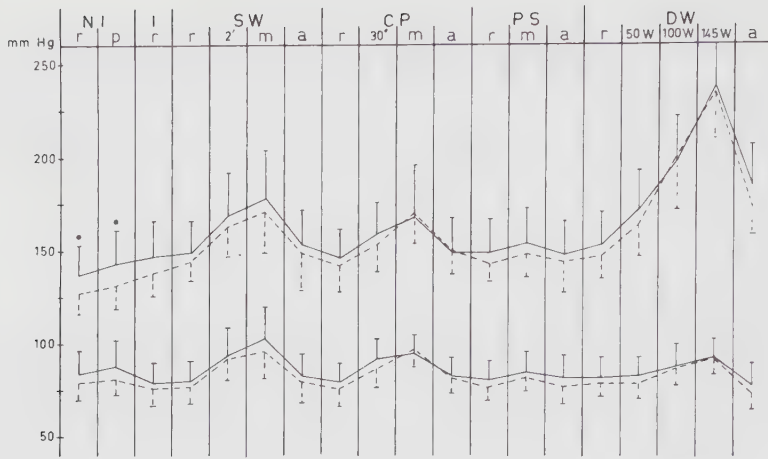


Fig. 1 illustrates blood pressure in offspring (—) and controls (---) during the procedures.

NI = non-invasive, I = invasive, SW = static muscle work, CP = cold pressure test, PS = psychological stress, DW = dynamic muscle work.

r = rest, p = pain, m = maximum, a = after the test.

$p < 0.05 = *$.

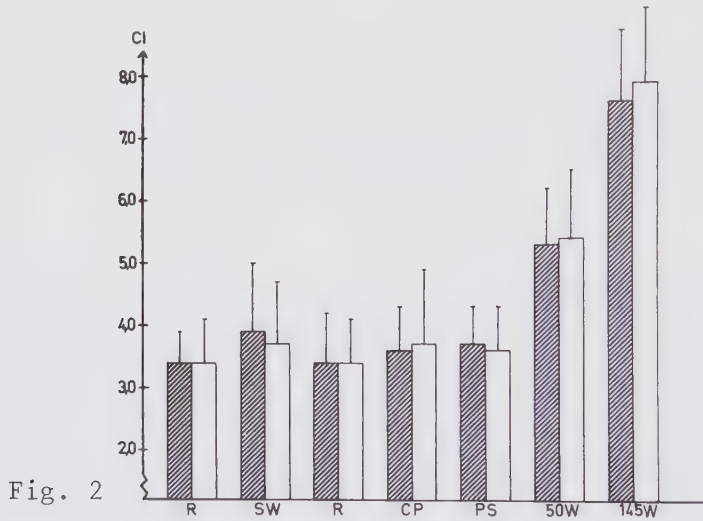
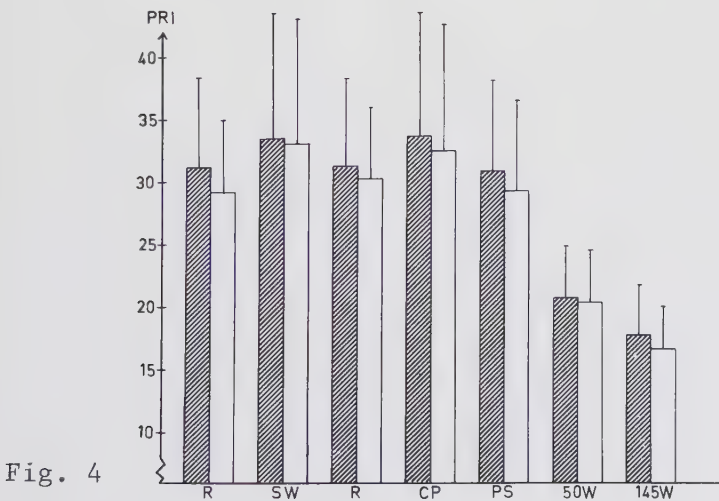
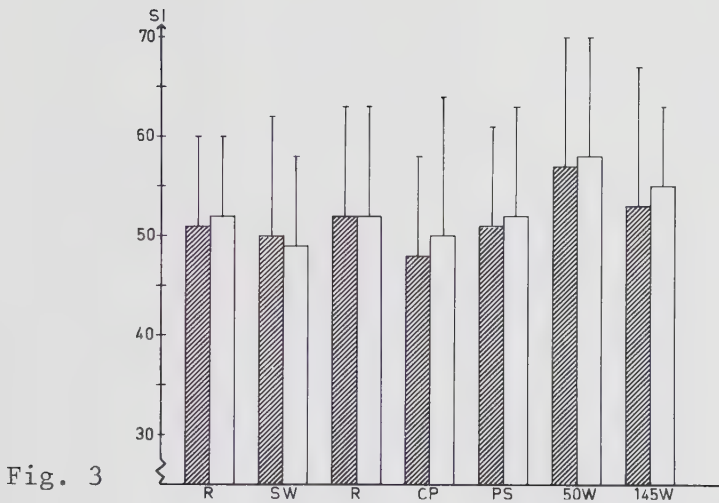


Fig. 2



Figs. 2, 3 and 4 illustrate cardiac index, stroke index and peripheral vascular resistance, respectively, in offspring (filled staples) and controls.

R = resting supine position, SW = static muscle work, R = at rest before cold pressure test, CP = at 30 seconds cold pressure test, PS = psychological stress, 50W and 145W = dynamic muscle work.

Table II. Blood gases, pO_2 , pCO_2 (kPa), pH and standard bicarbonate (stand. bic.) (mmol/l) in offspring (O) and controls (C) at rest (R), static muscle work (SW), rest before cold pressure (R), cold pressure 30" (CP), psychological stress (PS), dynamic muscle work 50W and 145W.
 $p < 0.05 = *$

	R	SW	R	CP	PS	50W	145W
pO_2							
O	11.6	12.5	11.6	11.8	11.8	11.9	11.9
C	11.2	11.9	11.1	12.3	11.8	11.4	11.4
pCO_2							
O	5.1	5.0	5.2	5.0	5.2	5.3	5.0
C	5.3	5.3	5.5*	5.2	5.5*	5.5	5.4*
pH							
O	7.45	7.45	7.43	7.44	7.43	7.43	7.38
C	7.43	7.43	7.42	7.44	7.42	7.41	7.37
Stand.bic.							
O	25.2	24.5	24.9	24.4	24.9	24.8	20.9
C	25.4	24.8	24.9	25.0	25.1	24.7	22.0

4.8 mmol/l, respectively). These latter differences between offspring and controls did not, however, reach statistical significance.

Subdividing offspring in regard to PRI at rest

When subdividing offspring into two groups, over and under the median of PRI at rest, it was found that the group of offspring with high PRI was older than the group of offspring with low PRI (39.1 and 32.8 years, respectively, n.s.). SBP in each group was 154.8 and 138.5 mmHg ($p < 0.05$), DBP 84.8 and 72.2 mmHg, respectively ($p < 0.01$). No significant difference between the groups was found in HR (65.1 and 69.0/min). Offspring in the former group were shorter (172.7 and 178.6 cm, respectively, $p < 0.01$) but no significant difference in right arm triceps skinfold thickness was found between the groups (10.6 and 10.0 mm, respectively). Mean body weight was 0.7 kg higher in the group of relatives with low PRI. There was no significant difference in arterial blood pCO_2 between the groups, either at rest or during the tests.

Subdividing offspring in regard to highest and lowest SBP at rest

Subdividing offspring into two groups, $SBP \leq 135$ mmHg and ≥ 140 mmHg, two groups were formed with mean SBP 124 and 149 mmHg, respectively. Mean age in the groups was 34.2 and 37.4 years, respectively. No significant difference was found between the groups as regards CI or SI either at rest or during the procedures. PRI was systematically higher among the group of offspring with the highest SBP and the difference between the groups found at rest (2.5 units) remained during all procedures. Both at rest and during the tests, pCO_2 was lower among offspring with the highest SBP. During cold pressure test, the difference between the groups reached statistical significance ($p < 0.05$) but at heavy dynamic muscle work, the differences between the groups decreased.

Correlations

A number of possible correlations between BP, HR, CI and SI were studied. Scattered correlations between those variables were found both in offspring and controls, mostly without any clearly apparent biological interest. It seems, however, to be interesting and will also be further discussed below, that HR in offspring was significantly negatively correlated to SI during static muscle work ($r = -0.54$, $p < 0.01$), dynamic muscle work at 50W ($r = -0.65$, $p < 0.01$) and at 145W ($r = -0.85$, $p < 0.001$). Among controls no correlation was found between HR and SI.

DISCUSSION

In an earlier investigation on 307 individuals we found that the relatives had a significantly higher SBP and HR at rest, both compared to controls without heredity for hypertension and to a screened age and sex matched population (22). In a representative subgroup we found that the difference between relatives and controls in blood pressure and heart rate reaction was maintained during static muscle work and psychological stress, but had a tendency to be equalized during heavy dynamic muscle work (23).

The aim of this study was to investigate the haemodynamic mechanisms responsible for the differences found between the groups. The selection of offspring for this study was, however, not entirely representative of the whole population of relatives, since they all belonged to the families with the highest occurrence of hypertension and hypertensive diseases. At the first investigation no significant difference in BP and HR did, however, exist between all the male relatives and the present subgroup in this investigation (Table I). The small expected fall in HR and BP on repeated examinations was also found at the second and third investigation. The numerical figures were small but significant. The controls with no heredity for hypertension were, however, examined for the first or second time in this study, and thus the difference between the groups should have been greater. Since BP and HR are reported to increase during the day and were measured in the morning in the present investigation, but at noon in the first investigation, this could also explain the differences found (21).

The significantly lower mean values of $p\text{CO}_2$ in the arterial blood from offspring at rest during psychological stress and maximal dynamic work indicate a somewhat higher ventilation in these subjects. However, the mean values of standard bicarbonate are not higher but generally tend to be even lower in almost all situations, and with almost equal arterial pH, primary hyperventilation is probably not the explanation, or at least not the only one. A primary slight metabolic acidosis, chronically compensated for by hyperventilation in these offspring could be another possibility.

As reported earlier, an abnormal sodium metabolism and a significant negative correlation between the intracellular contents of sodium and potassium in erythrocytes has been shown in other subgroups of relatives from hypertensive families (10, 11, 12). A negative correlation between the intracellular contents of sodium and potassium in erythrocytes has also been found in healthy adults (1). Almost 50% of the relatives in the referred studies, however, had an intracellular sodium content above the highest normal level. This could indicate a primary abnormality in the $\text{Na}^+\text{K}^+\text{ATPase}$ system in some of the relatives. Considering the possibility that there is a high grade of structural similarity between the human $\text{Na}^+\text{K}^+\text{ATPase}$ and $\text{H}^+\text{K}^+\text{ATPase}$ enzyme complexes (16), an inherited abnormality in the intra- and extracellular distribution of protons (H^+) might be possible.

Differences found in BP and HR between offspring and controls in this investigation and in the investigation earlier performed on a larger group of relatives, were maintained during and after all procedures, except during heavy dynamic muscle work and the cold pressure test, where the differences were diminished. The results in this respect were highly similar to the larger study on 195 relatives and should be representative compared to that study.

Among all offspring in this study there was a significant negative correlation between PRI and body height ($r = -0.52$, $p < 0.01$). No significant correlation between these variables was found in controls. The significantly lower body height among offspring with high PRI was, however, an interesting finding.

In the whole material of male relatives ($n = 169$) earlier described (22), we thus made a comparison between the shortest ($\bar{X} = 169.8$ cm) and the tallest ($\bar{X} = 185.8$ cm) quartile. In this larger material we also found that relatives belonging to the "shortest quartile" had a higher BP (142.4/87.0 mmHg) and HR (76.4/min) compared to the "tallest quartile" (137.5/82.3 mmHg and 72.2/min, respectively). These differences between the quartiles did not, however, reach statistical significance. At present we have no clear explanation of this finding but it seems indicated to study these relationships further.

Stroke index was lower at rest in offspring than in controls. These differences were enhanced during heavy dynamic muscular work. When correlating the haemodynamic variables with BP and HR, we found a significant negative correlation between stroke index and HR in offspring but not in controls. No clear conclusion can be drawn from this finding, but it could be interpreted as an incapacity among offspring to increase stroke index when the load on the myocardium increases.

In another study (9) we found that the offspring here referred to had a lower plasma concentration of norepinephrine as compared to controls. The difference was statistically significant at the cold pressure test ($p < 0.05$).

We have also found that male offspring had an abnormal whole body and cellular (erythrocytes) turnover of ^{22}Na as compared to controls (10, 11, 12). The observed changes in the whole body turnover of sodium as well as in the red cells might indicate that the changes should not be entirely located to the red cell. If such changes are present in the arterial muscle cell and/or nerve terminals, they might influence both discharge and con-

traction, possibly by the effect on the organel cytosol calcium shift as discussed by Blaustein (3).

Most authors have centered their interest to so-called "borderline hypertensives", which means individuals with blood pressures oscillating between the normal and elevated. Follow-up studies have, however, yielded very diverging results concerning the risk of a later established hypertension, from no increased risk to the double (14). Individuals with "borderline hypertension" have been found to have an elevated cardiac output at rest and normal peripheral vascular resistance in comparison to controls (5, 14, 25, 26). The increase in blood pressure during muscle work in persons with borderline hypertension has not been found to differ from normotensive controls. Differences in cardiac output have been found to disappear during muscular work (15, 17, 18, 19, 27).

A total of six of our investigated offspring could be characterised as "borderline hypertensives" by definition, but their cardiac output at rest did not differ from that found among the rest of the investigated offspring. Peripheral vascular resistance was higher in the borderline group, both at rest and during the procedures.

In a comparison to other studies carried out on normotensive individuals, we found a good agreement between the cardiac output of our controls and of the normotensives in these materials (2). Lund-Johansen (20) has reported that in a ten-years-follow-up study of borderline hypertensives, only the individuals with initially normal cardiac output and an increased peripheral vascular resistance, increased their blood pressure at the second examination. Individuals with elevated cardiac output remained at the same blood pressure level 10 years later.

In summary, in this study also we could confirm that the blood pressure among offspring was constantly elevated during the provocation tests, except at cold pressure test and heavy dynamic muscular work. Stroke index was lower and peripheral vascular resistance higher among offspring as compared to controls. This could indicate an involvement of the myocardium. A connection might also exist between these findings and differences in

sodium turnover between offspring and controls. An abnormal and genetically derived high intracellular amount of sodium could lead to a chronically increased tone of the resistance and capacitance vessels. This might also give other effects on the haemodynamics, i.e. a central redistribution of the plasma volume and even a reduced plasma volume (5, 6, 7, 24, 25, 29, 30). Further studies on relatives of hypertensive individuals should deal with these questions.

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IV

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PLASMA VOLUME AND PLASMA VOLUME DISTRIBUTION AT REST, DURING MUSCULAR
WORK, COLD PRESSURE TEST AND PSYCHOLOGICAL STRESS IN MALE OFFSPRING TO
FAMILIES WITH A HEAVY AGGREGATION OF HYPERTENSION

Running headline: Plasma volume and its distribution in offspring to
hypertensive families

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ABSTRACT

Total and central plasma volume was measured in male offspring to hypertensive individuals, belonging to families with at least two generations suffering from essential hypertension. They were compared to age matched individuals with no known hypertension in their families for at least two generations. Central plasma volume was determined at rest and during muscle work, cold pressure test and psychological stress.

Offspring were found to have a significantly lower total plasma volume compared to controls. Central plasma volume was equal in offspring and controls. The quotient central/total plasma volume was thus higher in offspring, and the difference to controls was statistically significant during psychological stress and dynamic muscle work.

As possible reasons for the differences found between offspring and controls are discussed an increased transcapillary escape of plasma, an increased quotient intracellular/extracellular fluid and/or an increased tone of the capacitance vessels.

INTRODUCTION

In earlier studies on relatives of hypertensive families, we found a significantly higher systolic blood pressure and plasma albumin concentration among both male and female relatives of all ages as compared to a control group without heredity for hypertension as well as to a screened population (15). The higher blood pressure among relatives compared to controls was found to be due to a higher vascular resistance in the former group (16). In some studies on mild to moderate hypertensive individuals, it has been reported that these people have an increased vascular resistance, a decreased total plasma volume and an increased quotient central/total plasma volume (8, 20, 21, 23, 26).

The aim of this study was to investigate the plasma volume and its relation to blood pressure and haemodynamics (cardiac output, stroke volume and peripheral vascular resistance) and the plasma volume distribution in male offspring to hypertensive individuals belonging to families with a heavy aggregation of the disease.

MATERIAL AND METHODS

Material

This material was selected from male offspring of 106 hypertensive patients belonging to families with at least two generations suffering from essential hypertension. A total of 169 male relatives were examined with blood pressure at rest, heart rate and laboratory investigation (15). Male offspring from families where the incidence in hypertension was 50% among the family members were randomly selected for this investigation.

A total of 35 male offspring to hypertensive individuals were investigated, here called group I. From group I, 16 individuals were also examined with determination of the intravascular plasma volume distribution at rest, static muscle work, cold pressure test and psychological stress. This group of relatives was called group II.

As illustrated in Table I, there were no significant differences in blood pressure, HR, mean age, height, weight or hematocrit between the total group of investigated male relatives ($n = 169$) and group I ($n = 35$) or group II ($n = 16$). Plasma albumin was significantly lower in group I ($p < 0.01$) as compared to the total group of male relatives, but no significant difference was found compared to group II.

The controls to group I consisted of 25 normotensive male volunteers, to group II of 13 male volunteers, all without any known hypertension in their families for at least two generations. The subjects were all informed of the nature and purpose of the study and their voluntary consent was obtained.

Methods

All studies were done in the morning. The individuals had abstained from food and smoking for at least 8 hours before the investigation. After 10 minutes rest in the supine position, blood pressure (BP) and heart rate (HR) were measured according to procedures earlier described (15). After 30 min rest, 10 ml of the indicator Evans blue was injected intravenously into an arm for determination of total plasma volume (TPV). After 15 min equilibrium, blood samples were taken from a vein of the other arm.

In group II we also determined the central plasma volume, and cardiac output at rest, during static and dynamic muscle work, cold pressure test and psychological stress. The methods for these procedures have been described in detail elsewhere (16). In group II a polyethylene catheter (PE 160) was inserted into arteria brachialis after previous anesthesia, the tip being placed in the axillary region. The tip of a venous polyethylene catheter was placed in the right atrium under X-ray control.

Cardiac index (CI) was calculated (CO/m^2) ($\text{l}/\text{min}/\text{m}^2$), using dye dilution technique with bromsulphthalein (BSP) as the indicator (10). Mean arterial pressure (MAP) in group I was calculated according to the formula $\text{SBP}-\text{DBP}/3$ plus DBP, in group II by electrical integration over a period including at least two respiratory cycles of the pressure curves. The peripheral vascular resistance (PRI) was calculated as MAP/CI . Stroke index (SI) was calculated by dividing CI with HR, which was obtained from ECG. The plasma volume between the tip of the catheter located in the axillary region of the brachial artery and the venous catheter located with the tip in the right atrium, was called the central plasma volume (CPV). CPV was calculated from the dye dilution curves according to the formula $\text{cardiac output (CO)} \times \text{mean transit time (22)}$. Both total and central plasma volumes were corrected for cm height.

Standard statistical methods were used (Student's t-test, $\bar{X} \pm 1 \text{ SD}$). Unless otherwise stated, no significant differences were found.

RESULTS

Group I

TPV was significantly lower in offspring, 16.5 ml/cm body height compared to controls 18.4 ml/cm ($p < 0.001$). Blood volume was also significantly lower in offspring than in controls (27.3 and 30.2 ml/cm; $p < 0.01$). There was a significant difference between offspring and controls in SBP ($p < 0.001$), HR ($p < 0.001$) and plasma albumin concentration ($p < 0.05$).

In a subgroup with $\text{DBP} \leq 85 \text{ mmHg}$ there was also a significant difference ($p < 0.05$) in TPV between offspring ($n = 23$; $\bar{X} \text{ DBP} = 75 \text{ mmHg}$; $\text{TPV} = 16.9 \text{ ml/cm}$) and controls ($n = 22$; $\bar{X} \text{ DBP} = 74 \text{ mmHg}$; $\text{TPV} = 18.4 \text{ ml/cm}$). Blood volume was also significantly lower in offspring than in controls (27.4 and 31.3 ml/cm; $p < 0.01$). When offspring and controls were subdivided with regard to SBP at rest $\leq 140 \text{ mmHg}$, two groups were formed with 24 individuals in each ($\bar{X} \text{ SBP } 131 \text{ and } 125 \text{ mmHg}$, respectively). TPV among offspring was 16.8 ml/cm, among controls 18.5 ml/cm ($p < 0.001$).

Table I. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), height, weight, hematocrit, albumin, total plasma volume and blood volume (TPV and TBV, respectively), central plasma volume (CPV), cardiac index (CI) and peripheral vascular resistance (PRI) in offspring and controls of group I and II, respectively.
 $p < 0.001 = ***$, $p < 0.01 = **$, $p < 0.05 = *$

	SBP	DBP	HR	Age	Height	Weight	Hematocrit	Albumin	TPV	TBV	CPV	CI	PRI
Total group of investigated male relatives (n = 169)	139 ±14.7	83 ±12.3	75 ±11.0	35 ±12.7	178 ±6.3	76 ±11.2	44 ±2.7	49 ±3.2	-	-	-	-	-
								**					
Offspring group I (n = 35)	139 ±14.8	82 ±12.9	76 ±8.2	34 ±10.4	178 ±6.8	80 ±12.3	43 ±2.6	47 ±2.7	16.5 ±1.5	27.3 ±2.6	-	-	-
	***		***					*	***	**			
Controls to group I (n = 25)	126 ±10.0	77 ±8.0	64 ±8.7	31 ±8.2	179 ±6.1	79 ±11.9	43 ±2.9	45 ±2.9	18.4 ±2.6	30.2 ±4.5	-	-	-
Offspring group II (n = 16)	142 ±14.7	87 ±12.5	76 ±9.8	40 ±9.3	175 ±5.4	79 ±8.4	44 ±2.7	48 ±3.2	16.5 ±1.1	27.4 ±2.6	6.8 ±1.3	3.3 ±0.6	32.2 ±8.6
	**		**					*	**	**			
Controls to group II (n = 13)	127 ±8.1	80 ±6.9	65 ±9.8	34 ±9.4	177 ±5.3	82 ±13.8	43 ±2.2	45 ±3.0	19.1 ±2.9	31.3 ±4.8	6.9 ±1.1	3.4 ±0.6	30.3 ±5.4

Correlation between plasma volume and blood pressure, heart rate, albumin and hematocrit

In offspring, there was a significant negative correlation between plasma volume and SBP ($r = -0.38$, $p < 0.05$), DBP ($r = -0.44$, $p < 0.05$) and MAP ($r = -0.37$, $p < 0.05$). No significant correlation was found between plasma volume and blood pressure in controls. No correlation was found between plasma volume and heart rate, hematocrit and albumin either among offspring or among controls. No correlation between TPV and pulse pressure was found in offspring or controls.

Group II

Central plasma volume (CPV) in the resting supine position was equal in offspring and controls (6.8 and 6.9 ml/cm, n.s.). No significant difference was found in CI or PRI between offspring and controls.

Also in group II, TPV was significantly lower in offspring than in controls, 16.5 and 19.1 ml/cm, respectively ($p < 0.01$). Total blood volume in offspring was 27.4 ml/cm, in controls 31.3 ml/cm ($p < 0.01$).

The offspring in group II had a significantly higher SBP ($p < 0.01$), HR ($p < 0.01$) and plasma albumin concentration ($p < 0.05$) as compared to controls.

Correlations

No significant correlation was found between TPV or CPV and blood pressure, heart rate, plasma albumin or hematocrit, either in offspring or in controls of group II. No significant correlation was found between TPV and the haemodynamic variables CI, PRI or SI.

CPV during the tests

As illustrated in Fig. 1, the quotient between CPV and TPV was higher in offspring than in controls.

At psychological stress and dynamic muscle work, the difference to controls was significant. Among offspring, the quotient increased 26.5% from rest to 50W dynamic muscle work ($p < 0.001$), while this increase was 20.3% ($p < 0.05$) in controls.

From rest to 145W the quotient increased 45.6% and 39.1%, respectively ($p < 0.001$).

DISCUSSION

In some studies performed on mildly to moderately hypertensive individuals, a decreased plasma and blood volume has been demonstrated (8, 20, 23, 24, 25, 26) and also an increased quotient central/total plasma and blood volume (7, 21, 27) compared to normotensive controls. Other studies have, however, not been able to verify these findings (1, 5, 9).

The total plasma volume was in some studies found to be inversely correlated to blood pressure (14, 23), but here too the results are diverging (13, 28). Parving (19) found that the transcapillary escape of albumin was increased in hypertensives, who also had a significantly decreased plasma volume as compared to normotensives. The differences described between the various studies could be due to different severity of the hypertensive disease at the time of the examination, different measuring procedures, body position and also the time of the day when the investigation was performed (5).

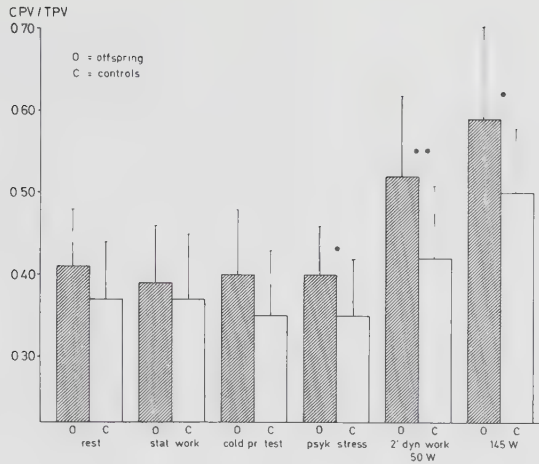


Fig. 1. Quotient central plasma volume (CPV)/total plasma volume (TPV) in offspring and controls during the tests.

$p < 0.01 = **$, $p < 0.05 = *$

We found in the earlier investigation on offspring to patients with hypertension, belonging to families with a heavy aggregation of the disease, that they had an increased vascular resistance at rest and during several tests. Since a decreased TPV and increased ratio CPV/TPV has been described in mild hypertensive individuals, we decided to measure TPV and CPV during the same procedures as described in our earlier studies (16, 17). The subgroup chosen for this study was fully representative as compared to the total group of investigated male relatives concerning age, height, weight, blood pressure and heart rate (Table I). The offspring had a significantly lower total plasma volume than the controls as described in a preliminary work (18). The measuring procedures were identical in the groups.

In a comparison to other studies performed on normotensive and hypertensive individuals, we found a very good agreement between the plasma volume in our controls and the plasma volume of normotensives in these materials (3).

Plasma volume is mostly corrected to minimize influence of body surface and weight. In this investigation we decided to use ml/cm height. Since body height is a constant factor, this parameter is well suited to planned long term follow-up studies. Also when corrected for other variables, ml/kg weight or l/m^2 body surface, the significant differences between offspring and controls remained unchanged.

Since there were significant differences between the groups in total blood volume but no difference in hematocrit, it is not probable that the differences in plasma volume are due to transcapillary filtration. Also in a comparison between strictly normotensive offspring and controls, a significant lower plasma volume was found in the former group. This indicates that the blood pressure level itself is of minor importance for the differences in plasma volume.

In other studies on subgroups of the offspring in this study, we have found an abnormally slow whole body and cellular (erythrocytes) turnover of ^{22}Na (11, 12). If such changes are present in the smooth muscle cell and/or nerve terminal, they might influence both discharge and contraction (4, 6), giving an increased vascular tone with a central redistribution of plasma volume. The offspring in this study, had both at rest and during exercise a higher ratio central/total plasma volume as compared to controls. During dynamic muscle work, the increase of the quotient was higher in offspring ($p < 0.001$) as compared to controls ($p < 0.05$). This could depend on a more pronounced increase of the tone of the capacitance vessels in offspring. The decreased plasma volume found in offspring could be a result of a secondary adaption to this increased tone. The decreased plasma volume could also be due to an increased ratio intracellular/extracellular water as discussed earlier (11, 12). There have, to our knowledge, been no other comparable study on plasma volume in members of families heavily loaded with hypertension.

Bianci (2) investigated children from parents with mild blood pressure elevation ($> 155/95$). He found that these children had a plasma volume which did not significantly differ from that of children from normotensive parents ($\leq 140/90$). The mildly elevated blood pressure which was reported in families of the study by Bianci, is in no way comparable to the degree of hypertensive diseases and the risk of a future hypertension which is present in families of our study.

The decreased plasma volume in normotensive individuals with heredity for hypertension, might be a marker for an increased risk of hypertension and could be helpful for future investigations in the etiology and pathophysiology of essential hypertension.

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CATECHOLAMINES AND RENIN ACTIVITY IN PLASMA AT REST, STATIC ARMWORK AND
COLD PRESSURE TEST IN OFFSPRING TO ESSENTIAL HYPERTENSIVE PATIENTS

By

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Key words: Offspring - Essential Hypertension - Submaximal stress -
Plasma catecholamines - Plasma renin activity.

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ABSTRACT

1. Essential hypertension (EH) has in the past often been suspected of being due to over-activity of the sympathetic nervous system, and elevations in plasma levels of catecholamines (norepinephrine (NE) and epinephrine (E)) and the total plasma renin activity (PRA) have been taken as markers for this assumption.
2. We have made a hemodynamic investigation in which the levels of NE, E and PRA have been measured during standardized conditions - (supine rest, static arm-work and cold pressure test) - in 23 normotensive or mildly hypertensive male offspring to patients with EH. The controls were 15 normotensive and age-matched volunteers without a history of EH in their families.
3. At rest, the plasma volume (PV) was found to be significantly lower ($p < 0.001$) in offspring.
4. Epinephrine was significantly correlated to the cardiac index (CI) in both groups during rest and both stress situations. NE was significantly lower ($p < 0.05$) in male offspring during the cold pressure test. No difference in the mean levels of PRA was found between the two groups in any situation.
5. The decreased plasma volume found in male offspring could indicate an abnormal distribution of sodium and water between the extra- and intracellular phases based on genetic cellular differences in sodium handling.

INTRODUCTION

It is generally accepted that both the sympathetic nervous system and the renin-angiotensin-aldosterone system are involved in the blood pressure (BP) regulation in normal man (1, 2, 3). However, in patients with EH, divergent results as to the role of plasma catecholamines (4-11) and the renin-angiotensin-aldosterone system have been presented (12-14). The conclusion from these results appears to be that the patient and control materials are different with respect to sex and age (3, 13), severity of hypertension (3, 15, 16) or alcohol consumption (10, 17-19).

In 1961 Doyle and Fraser (20) showed that iv injections of NE in normotensive offspring to patients with EH resulted in a greater BP-rise than in controls born of normotensive parents. Studying normotensive offspring (adolescents) to hypertensive patients, Falkner et al. (21) found NE to be increased at rest and during mental stress as compared to controls, but this could not be verified in the study by Bianchi et al. (22). The latter investigators also found PRA to be normal in offspring in contrast to the findings by Fasola et al. (23) who studied offspring during rest and supine hemodynamic work.

From the recent works by Luft et al. (24) and Romoff et al. (25) it is also obvious that studies of NE and E in plasma and urine have to be related to the status of sodium intake (urinary excretion), which is also true for the study of PRA (13).

In earlier reports (26, 27) we have shown that normotensive or borderline hypertensive offspring (especially males) have both abnormal whole-body and cellular metabolisms of sodium indicating a markedly increased total amount of intracellular sodium. Increased amount of intracellular sodium and water in various tissues taken from deceased hypertensive patients has also been shown in the early reports by Tobian and Binion (28) and also recently by Bauer et al. (29) in mildly, but sustained hypertensive patients.

As also published in a preliminary report (30) we have in the offspring reported here and during an invasive investigation studied the hemodynamic response during both rest and different situations of stress inductions. The BP elevation during static armwork as well as the cold pressure test is very rapid as reported by others (31, 32) and our aim was therefore to determine if this BP rise was accompanied with simultaneous changes in catecholamines and PRA in offspring to hypertensive patients and compared with controls without heredity for EH.

MATERIAL

A group of 307 non-treated first-to-third-degree relatives of 106 hypertensive probands were studied at the Division of Preventive Medicine, Malmö General Hospital. They were 20 to 60 years of age (27, 30). Selected at random from the 52 families where at least 50% of the members during two generations had been treated for hypertension, 23 normotensive or mildly hypertensive males (offspring to probands) aged below 60 were investigated in this survey. Four males had a supine diastolic blood pressure (DBP) of at least 95 mmHg (95, 95, 100 and 105) and nine standing DBP in the same range. Fifteen normotensive and age-matched male volunteers without histories of hypertension in their families were investigated as controls (Table 1). Only two of these controls worked at the hospital. Their agreement was given as a written consent.

METHODS

Procedure

The subjects were instructed to collect all urine during a 24 hours' period prior to the investigation and to abstain from smoking 8 hours before the study. At 9 a.m. in the morning the fasting subjects arrived at the hospital and were placed on a catheterization table to rest. Ten minutes later, their values of indirect BP were measured with an appropriate cuff. After 10 minutes of additional rest, each subject was catheterized in the left arm through an antecubital vein as well as in the brachial artery as described before (30). After further 20 minutes of rest, venous blood samples were drawn and the plasma volume (Evans blue dye dilution technique) (l/m^2) and cardiac index (CI) ($l/min/m^2$ body surface) was determined with the Bromsulphalein dye dilution technique (30). Each subject was then tested with a handgrip dynamometer using the right arm and the maximal force noted. Static handwork (armwork) was then performed for 5 minutes at 30% of the maximal level. After 3 minutes of work, a CI measurement was made and blood samples taken. The subjects then rested until basal levels of BP and heart rate (HR) were obtained (5-10 minutes). The right hand was then placed up to the wrist in ice-water ($0-2^{\circ}C$) for 2 minutes and blood samples were again taken together with a measurement of CI.

Table 1. The indirectly measured blood pressure and heart rate, age, height and weight and 24 h sodium excretion in the whole group of male relatives (n = 169), in 23 male offspring at the 1. and 2. (present) investigation as well as in the 15 controls without heredity for hypertension.
p < 0.05 = *

	SBP	DBP	HR	Age	Height	Weight	Sodium excretion
Whole group of male relatives 1. investigation. Resting supine 10' n = 169	139 ± 14.7	83 ± 12.3	75 ± 11.0	35 ± 12.7	178 ± 6.3	76 ± 11.2	152 ± 40
Present subgroup at 1. investigation. Resting supine 10' n = 23	140 ± 12.1	83 ± 11.0	75 ± 10.2	35 ± 10.0	177 ± 6.2	75 ± 8.5	161 ± 42
This investigation. Resting supine 10' n = 23	138 ± 11.2	83 ± 10.0	70 ± 10.3				170 ± 44
Genetic controls n = 15	127 ± 11.1	79 ± 9.2	69 ± 8.2	33 ± 9.3	177 ± 6.0	80 ± 13.8	162 ± 43

Laboratory analysis

After storing the plasma in a deep-freezer (-70°C), NE and E (ng/ml) were analyzed blindly with a double isotope derivation technique (33). PRA (pcat/l) was also measured blindly in plasma with a radioimmunoassay method (34, 13) after storage at -20°C . The concentration of sodium in urine was measured with routine flame photometry.

Statistical methods

The significance of the difference of the means was estimated using Student's t-test. All values are given as $\bar{X} \pm 1$ SD. Correlation analysis was carried out assuming linear regression. The one-way covariance test was used as an appropriate check of the independence of the variables.

RESULTS

Plasma catecholamines

Plasma catecholamines were analysed during rest, static work and the cold pressure test (Table 1, fig. 1). At rest NE was significantly related to systolic blood pressure (SBP) in offspring ($r = 0.55$, $p < 0.05$) but not in controls. Age and NE were positively correlated in both groups, but in offspring at a significant level only during static work ($r = 0.54$, $p < 0.05$) and in controls only during the cold pressure test ($r = 0.53$, $p < 0.05$). During the cold pressure test, NE was significantly lower in offspring (42%, $p < 0.05$) (Table 1, fig. 1). With the one-way covariance test (age-NE), the difference compared to controls was even more marked ($F = 7.85$, $p < 0.01$) and this was also true after correction for urinary sodium excretion (mmol/24 h; $p < 0.01$).

There was a highly significant correlation between E and CI in the two groups both at rest and during the two provocation tests (fig. 2). Neither at rest nor during any form of stress induction could any significant difference in the mean values of E between offspring and controls be observed.

Table 2. Intravascular measured physical and biochemical variables during rest, static armwork and the cold pressure test ($p < 0.01$).

$p < 0.001 = ***$, $p < 0.05 = *$

		Offspring		Controls	
Resting 30'	HR/min	67	± 10	68	± 10
	SBP mmHg	143	± 18	139	± 12
	DBP mmHg	77	± 11	76	± 9
	CI l/m^2	3.4	± 0.5	3.4	± 0.7
	PRA $pcat/l$	0.53	± 0.31	0.51	± 0.59
	NE ng/ml	0.21	± 0.13	0.29	± 0.17
	E ng/ml	0.06	± 0.04	0.06	± 0.03
	PV l/m^2	1.53	± 0.11	***	1.76 ± 0.27
Static armwork	HR	76	± 15	76	± 13
	SBP	167	± 22	163	± 16
	DBP	92	± 12	92	± 11
	CI	3.7	± 0.9	3.7	± 1.0
	PRA	0.60	± 0.32	0.62	± 0.71
	NE	0.22	± 0.08	0.25	± 0.14
	E	0.08	± 0.04	0.07	± 0.05
Cold pressure test	HR	76	± 12	73	± 11
	SBP	158	± 18	153	± 14
	DBP	90	± 10	87	± 10
	CI	3.6	± 0.8	3.7	± 1.2
	PRA	0.64	± 0.50	0.46	± 0.37
	NE	0.27	± 0.08	*	0.36 ± 0.18
	E	0.06	± 0.04	0.06	± 0.01

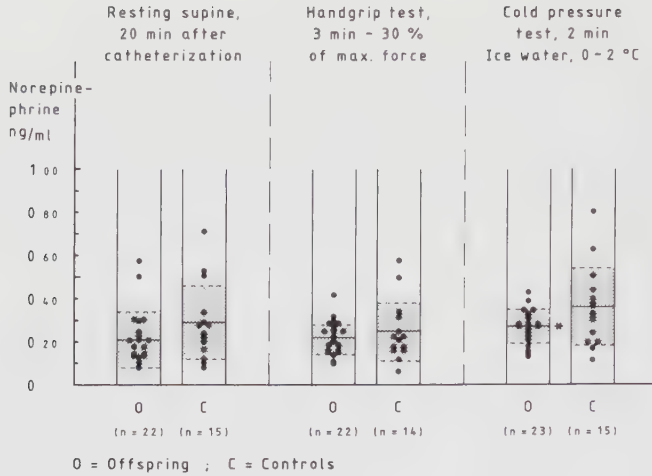


Fig. 1. The individual values and means in both groups of norepinephrine during rest, static armwork and cold pressure test. Only during the latter a significant difference was noted. Corrected for sodium excretion and age the difference was even more marked ($F = 7.85$, $p < 0.01$)

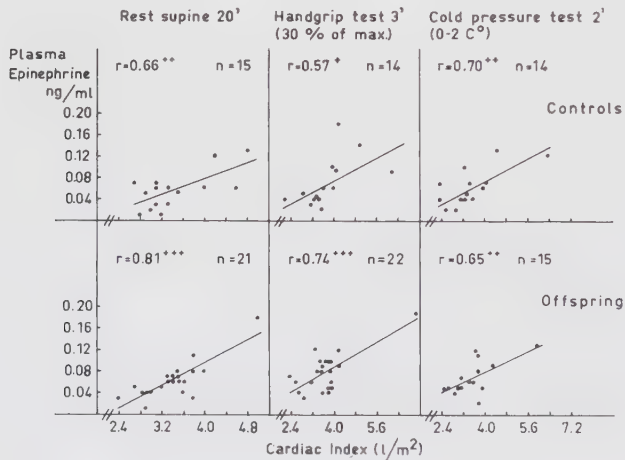


Fig. 2. Significant positive correlations between cardiac index and epinephrine were found in both groups during all studied situations. Even without the out-layers in the offspring group, the correlations were significant, however, at a lower level of significance. No difference in the mean values were noted between the groups at either situation (Table 2).

Plasma renin activity (PRA)

At all situations tested there was no significant difference between offspring and controls in the mean PRA value (Table 2). Only during the cold pressure test, was PRA significantly correlated to CI ($r = 0.53$, $p < 0.05$) in offspring, but not in controls ($r = 0.49$).

There was no significant correlation between PRA and urinary sodium, age, body weight, body surface area, BP, HR or PV in any group.

Plasma volume, hemodynamic parameters and urinary sodium excretion

The plasma volume was considerably and significantly lower (15%) ($p < 0.001$) in offspring (Table 1). BP, HR and CI in the two groups at rest, static work and the cold pressure test were consistent with the results in the previous report (30) and no significant differences were found. Nor could any significant difference in urinary sodium excretion be observed (Table 1).

DISCUSSION

Attempts to achieve some understanding of the role of the sympathetic nervous system in EH have been performed in both experimental and in human hypertension (35). To study possible prehypertensive states, several investigators (36, 37) have used a material with younger individuals with slightly elevated BPs (i.e. borderline hypertension, labile hypertension), but have also pointed out that the percentage of patients who actually later got treatment for hypertension is relatively small - 10-30% after longterm follow-up. Our choice as presented here was offspring to patients with an established and treated EH also belonging to families with a heavy aggregation of EH with its morbid/lethal manifestations, a material which seems to reveal several significant differences (26, 27, 30, 38), all of them also demonstrated in patients with EH.

Our aim in this study therefore was to evaluate the possible role of the sympathetic nervous system in the BP-rise during different situations using the hemodynamic variables HR, BP, PV or CI as well as the plasma variables NE, E and PRA. It is well known that the reactivity of plasma catecholamines is very rapid and that the rise in plasma occurs within some few minutes after the initiation of some stress induction such as the cold pressure test (32) or static armwork (39) and that the plasma half-life of both NE and E is short - 2-3 minutes (1, 2). The elevation of PRA during stress seems to be relatively low - especially in the supine position - and with a substantial delay (10-20 minutes) (31, 39). The plasma half-life of PRA is estimated to be around 20-30 minutes (3). In this study the stress induction sequence was the same in all the individuals and the time-lag between the tests was exactly the same in both groups. Only HR and BP were followed continuously as reported before (30). Unfortunately, we did not have the laboratory capacity to follow NE, E and PRA in plasma during the whole stress induction. However, we also consider the resting values to be the most important for the interpretation of the results, because of the uncertainty of relating NE, E or PRA in plasma during stress to other hemodynamic variables (2, 3). It was our belief that these offspring would show marked elevations of NE, E and PRA as previously indicated (21, 23, 6), but this was not found. Despite the significant rise in HR and BP related to rest, NE was significantly lower in offspring during the cold pressure test. In controls, during the cold pressure test, the plasma level of NE was significantly higher than during static work (44%, $p < 0.05$) and the mean values found are consistent with those found by Winer et al. (32) who measured NE after 3 minutes at the end of the cold pressure test.

The rise in PRA during supine stress was very moderate as also pointed out by others (31, 39). The increase in plasma PRA after the initiation of some stress may last for 10-20 minutes (31) and the fall after removal of the stress may also be very slow. In our case, the whole procedure with both stress situations lasted for about 20 minutes, but we could not see any significant difference or rise and hence it seems as if PRA is not involved in the acute or stress-induced rise in BP or at any rate certainly not in the supine situation. The four individuals in the offspring group who were mildly hypertensive did not differ from the whole group in any variables measured.

The sodium balance or intake is important for the plasma levels of NE as has been shown in normal man (24, 25). The somewhat lower mean values of plasma NE in offspring - significantly so only during the cold pressure test - could be related to the abnormal whole body sodium turnover previously showed (26) as well as an increased intracellular (erythrocytes) sodium content (27). Also in mildly, but sustained hypertensive males an increased intracellular water (sodium?) content has been found (28).

The repeated finding that plasma E is significantly correlated to CI in both groups during all three situations could indicate that this is a physiological feature as has been shown for HR and CI (41). This latter feature could also be the reason why Franco-Morelli et al. (6) found increased levels of E in borderline or labile hypertensive patients for whom elevated levels of CI also have been demonstrated (42).

The decreased PV (30), the prolonged whole-body turnover of ^{22}Na (26) and the increased content of sodium in erythrocytes (27) in these offspring to hypertensive patients, could indicate an abnormal balance of sodium (and water) between the intra- and extracellular phases, especially in male offspring. Whether such an altered regulation of the sodium volume is due to primary abnormalities at the cell-membrane level (44) or is of a more static intracellular nature (27) or even both remains to be elucidated. An increased vascular reactivity to NE, E and PRA, which could be related to the intracellular sodium as mentioned above, could explain our here reported findings and also go along with the findings by Doyle and Fraser (20), who investigated the same model. In one work by Nazar et al. (11) it has been shown that plasma NE during sustained handgrip-test for 6-7 minutes was significantly lower at the end of the test in the patients with sustained EH as opposed to controls. So even though the plasma level of NE in the early phase of a possible sustained EH is not elevated and may even be lower, the role of NE in the regulation of BP at the synaptic cleft or nerve terminal is still very important - perhaps especially so in connection with abnormal intracellular (i.e. smooth muscle cells in the resistance vessels) ratios of unbound sodium and calcium ions or their shifts over the membrane (45).

ADDENDUM

This study was started in 1976 and finished during 1979 and during this period the BP rose further in eight offspring and six have now got treatment for sustained EH. The mean values of NE, E, PRA or PV of these eight patients did not differ significantly from the means of the whole group studied in this report.

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VI

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VENOUS VOLUME AND BLOOD FLOW IN HAND AT REST AND DURING PSYCHOLOGICAL STRESS
IN MALE RELATIVES, BELONGING TO FAMILIES WITH A HIGH FREQUENCY OF ESSENTIAL
HYPERTENSION

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ABSTRACT

In a previous study we observed a decreased plasma volume and an increased ratio central plasma volume/total plasma volume (CPV/TPV) among normotensive members of families with a high frequency of hypertension. Similar changes in plasma volume have previously been observed in both borderline and established hypertension (11, 21, 27, 30). It has been suggested that this change in plasma volume might be secondary to a reduced venous distensibility, which has been described both in borderline and established essential hypertension (24, 26, 29, 31). Since the vessels of the hand, both arteries and veins, are very sensitive to vasoconstrictor stimuli (32), we decided to study venous volume in the hand in normotensive relatives of hypertensive patients, using a plethysmographic technique described by Wood (33). The plethysmographic method was also used to measure hand blood flow and systolic blood pressure. Measurements were performed at rest as well as during a psychological stress test, which had previously been found to increase the ratio CPV/TPV.

MATERIAL

The material consisted of 19 male offspring to hypertensive individuals belonging to families with at least a two generation history of essential hypertension. The offspring in this study were all selected from an earlier reported study, in which we investigated 35 male offspring in regard to plasma volume and plasma volume distribution at rest and during several stress tests (18). For the present study we selected those 20 individuals, who had the lowest plasma volume in the previous investigation. In one case, the investigation was interrupted for technical reasons and we were not able to repeat the procedure. The controls were healthy male volunteers with no family history of hypertension for at least two generations. The subjects were all informed of the nature and purpose of the study and their voluntary consent was obtained.

Representativity and comparability between the groups (Table I)

The present subgroup of relatives selected for this study did not differ from the total number of male relatives at the first investigation concerning age, height, weight, systolic blood pressure, diastolic blood pressure or heart rate. Systolic blood pressure and heart rate had, however, decreased between the two investigations performed ($\bar{X}$ 36 months; systolic blood pressure $p < 0.01$; heart rate $p < 0.001$). The controls had never been investigated before. They were significantly younger than the relatives (5 years; $p < 0.05$), were taller (6 cm; $p < 0.01$) and had a significantly lower diastolic blood pressure (6 mmHg; $p < 0.05$).

Table I. Age, height, weight, systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR). Comparison is made between all male relatives at the first investigation and the present subgroup at the first and the present investigation.

$p < 0.01 = **$, $p < 0.05 = *$

	n	Age	Height	Weight	SBP	DBP	HR
All male relatives at the first investigation	169	35 ±12.7	178 ±6.3	76 ±11.2	139 ±14.7	83 ±12.3	75 ±11.0
The present subgroup at the first investigation	19	30 ±7.3	178 ±5.8	75 ±8.3	136 ±10.2 **	80 ±9.8	75 ±7.8 ***
The present subgroup at this investigation	19	33 ±8.1 * **	178 ±5.3 **	74 ±7.9	124 ±10.9	77 ±7.8 *	63 ±9.2
Controls	19	28 ±5.3	184 ±5.6	77 ±7.8	124 ±9.5	71 ±7.0	67 ±11.8

METHODS

All studies were performed in the morning. The individuals had been requested to abstain from food and smoking for at least eight hours before the investigation. After ten minutes' rest in the supine position, blood pressure and heart rate were measured; after a further ten minutes' rest, Evans blue was injected to determine plasma volume. All these measurements were obtained using procedures previously described (15, 18). Venous volume and blood flow was determined according to Wood (33). The individuals were lying on a couch with both arms 10 cm above heart level. The blood flow was determined in the left hand. The volume of the plethysmograph was 1695 ml. Thin latex gloves were glued to diaphragms of 3 mm thick rubber at the proximal end. The diaphragms were supported from the outside by adjustable steel plates. In order to prevent protrusion of the thin sleeve underneath the steel plate, pieces of thin plastic material were cut and inserted. A piston recorder was attached to the expansion chamber with polyethylene tubes. A counter balanced frontal writing ink pen was fastened on to the piston recorder. The recordings were made on paper on a rotating drum, which could be set at various speeds.

Venous volume (30) was measured using a cuff pressure of 60 mmHg and a water pressure in the plethysmograph of 30 mmHg. The effective venous pressure was thus 30 mmHg. The temperature in the plethysmograph was 42°C. No measurement started until at least 20 minutes after the water had reached the desired temperature. Calibration was performed with water via the plethysmograph. An increase of 1 ml in volume usually corresponded to a 3-4 mm increase in height of the recording. The room temperature varied between 22°C and 24°C. The basal flow reported was the mean value of three consecutive identical curves at rest.

After the basal measurements of blood flow had been performed a psychological stress test was made by using a binary choice generator. The individuals were wearing ear phones. In each ear they heard low and high tones, respectively, which were given irregularly, but at fixed intervals. When a low tone was heard in the ear phone, the individuals were requested to press a button with the left foot, and for a high frequency tone to press with the right foot. The intervals between the signals were successively decreased. Blood flow and venous volume were measured during 4 minutes exposition to the stress stimuli. Systolic blood pressure was obtained from the flow curves. The vascular resi-

stance was calculated by dividing systolic blood pressure with blood flow. Standard statistical methods were used (Student's t-test). Unless otherwise stated, no significant differences were found.

RESULTS (Table II)

Plasma volume was significantly lower in relatives as compared to controls (15.8 and 16.8 ml/cm; $p < 0.05$). Venous volume was slightly lower in relatives as compared to controls, both at rest and during the tests, but the differences were too small to reach statistical significance. During psychological stress, venous volume decreased 37% in relatives and 35% in controls. The time for reaching pre-stress levels of venous volume after the test was 3.2 minutes in relatives and 2.8 minutes in controls. Hand blood flow at rest was higher in relatives as compared to controls. During psychological stress hand blood flow decreased by 33.9% in relatives and by 14.2% in controls. The time for reaching pre-stress levels of blood flow after stress was 2.7 minutes in relatives and 2.3 in controls. The vascular resistance was lower in relatives as compared to controls. None of the differences above, however, reached statistical significance. At psychological stress, the vascular resistance increased 87.2% in relatives and 17.6% in controls ($p < 0.05$). There was no correlation between venous volume or blood flow and blood pressure, heart rate and plasma volume, either in relatives or in controls.

DISCUSSION

Hypertensive rats (23) have been found to have a reduced visceral venous capacity, which persisted after reduction of the vasoconstrictor tone with sodium-nitroprusside, suggesting that factors other than active venoconstriction account, at least in part, for the results. An increased water, sodium and potassium content in both arteries and veins has been demonstrated in hypertensive rats with a decreased venous visceral capacity (19, 20). A decreased passive extensibility of portal vein strips has also been demonstrated in spontaneously hypertensive rats (5).

In human studies, venous distensibility in the extremities has been found to be decreased in subjects with essential hypertension (24, 26, 29, 31). Caliva (3) found that both digital venous pressure and vascular resistance were higher

Table II. Hand blood flow (HBF, ml/100 ml tissue/min) and venous volume (VV, ml/100 ml tissue) at rest, during stress and at 4 minutes after stress

	n	Rest		Stress		After stress	
		HBF	VV	HBF	VV	HBF	VV
Relatives	19	7.76 ±4.40	2.25 ±0.73	5.13 ±4.02	1.41 ±0.75	6.81 ±4.81	2.48 ±0.72
Controls	19	6.05 ±3.88	2.32 ±0.60	5.19 ±3.42	1.52 ±0.63	5.69 ±4.11	2.55 ±0.64

in hypertensives vs normotensives. In a recent study, Takeshita (26) investigated forearm venous distensibility in nine men with borderline hypertension with a plethysmographic method. Seven of the individuals had a family history of essential hypertension. The venous distensibility was significantly decreased in the borderline group as compared to controls. After injection of phentolamine, the venous distensibility was still less among the borderline hypertensives as compared to normotensives, suggesting that the decreased distensibility was only partly due to alpha adrenergic vasoconstriction

In our study we found only a slightly, not significantly, lower venous volume in skin tissue in relatives of hypertensive patients as compared to controls. It is thus not probable that changes in venous volume in skin could be responsible for the central redistribution of plasma earlier described, at least not among the relatives in this study. This indicates that the greater tendency to "centralize" plasma volume during stress, which we observed in our previous study (18), was due to venoconstriction in other veins, such as veins in the viscera or the muscles.

An unexpected finding was that the hand blood flow was higher in relatives, and vascular resistance thus lower. The increase in peripheral vascular resistance during psychological stress was, however, significantly higher in relatives. Sivertsson (25) found that young men with mild blood pressure elevation had a significantly higher vascular resistance in the hand at maximal vasodilatation as compared to normotensive controls. An interesting finding in that study was that the tendency to increase vascular resistance was more pronounced in individuals with a normal cardiac index. Ten of the investigated relatives in the present study had been examined invasively 3 years previously and at that time they were found to have a normal cardiac index but a slightly increased peripheral vascular resistance, both at rest and during the tests (17). No difference was, however, found between these relatives and the others either in venous volume, hand blood flow or vascular resistance in the present study.

A significantly higher increase in forearm vascular resistance to norepinephrine infusion has been reported in normotensive sons of hypertensive patients as compared to controls without heredity for hypertension (4). In other studies on relatives of hypertensive patients (10), we have found that they had a lower plasma concentration of norepinephrine as compared to controls. One might speculate whether the relatives in the present study had an increased sensitivity to

catecholamines. In other studies performed on relatives of hypertensive patients, we have reported an abnormally slow whole body and cellular (erythrocytes) turnover of ^{22}Na (7, 8, 9). The sodium balance seems to be of great importance for the vascular reactivity (6). An abnormal and genetically derived high intracellular amount of sodium might give an increased ratio intracellular/extracellular water. If this mechanism is present in the cells of the human venous walls as has been demonstrated in arteries of essential hypertensive subjects (1, 28), a decreased compliance of the veins could be the result.

In a study by Mason (14) on the vascular dynamics of the forearm, intravenous infusion of ouabain, usually used in experimental work to decrease the activity of the sodium pump, resulted in a fall in forearm blood flow and an increase in venous tone and vascular resistance. An increased intracellular sodium/potassium ratio might also increase the ratio free calcium/bound calcium (2), resulting in an increased smooth muscle tone and even increased sensitivity to catecholamines.

In summary, the statistically higher ratio CPV/TPV found in relatives of hypertensive patients during psychological stress could not be explained by a reduced venous volume in skin tissue. It is probable, that the visceral or muscular capacitance vessels are responsible for the central shift of blood volume. A greater increase in vascular resistance to stress stimuli found among normotensive relatives to hypertensive patients in this study, might speak in favour of both metabolic and hemodynamic changes being present in individuals prone to hypertension.

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